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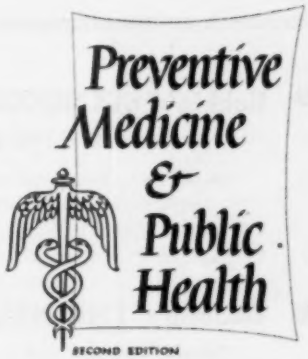

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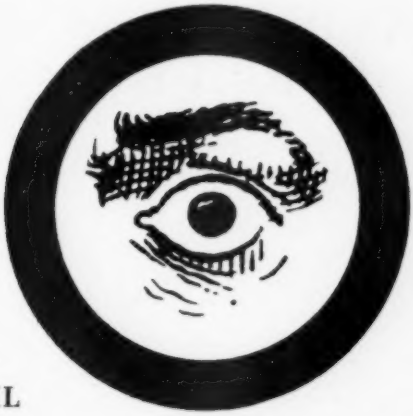

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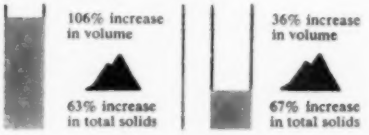

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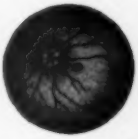

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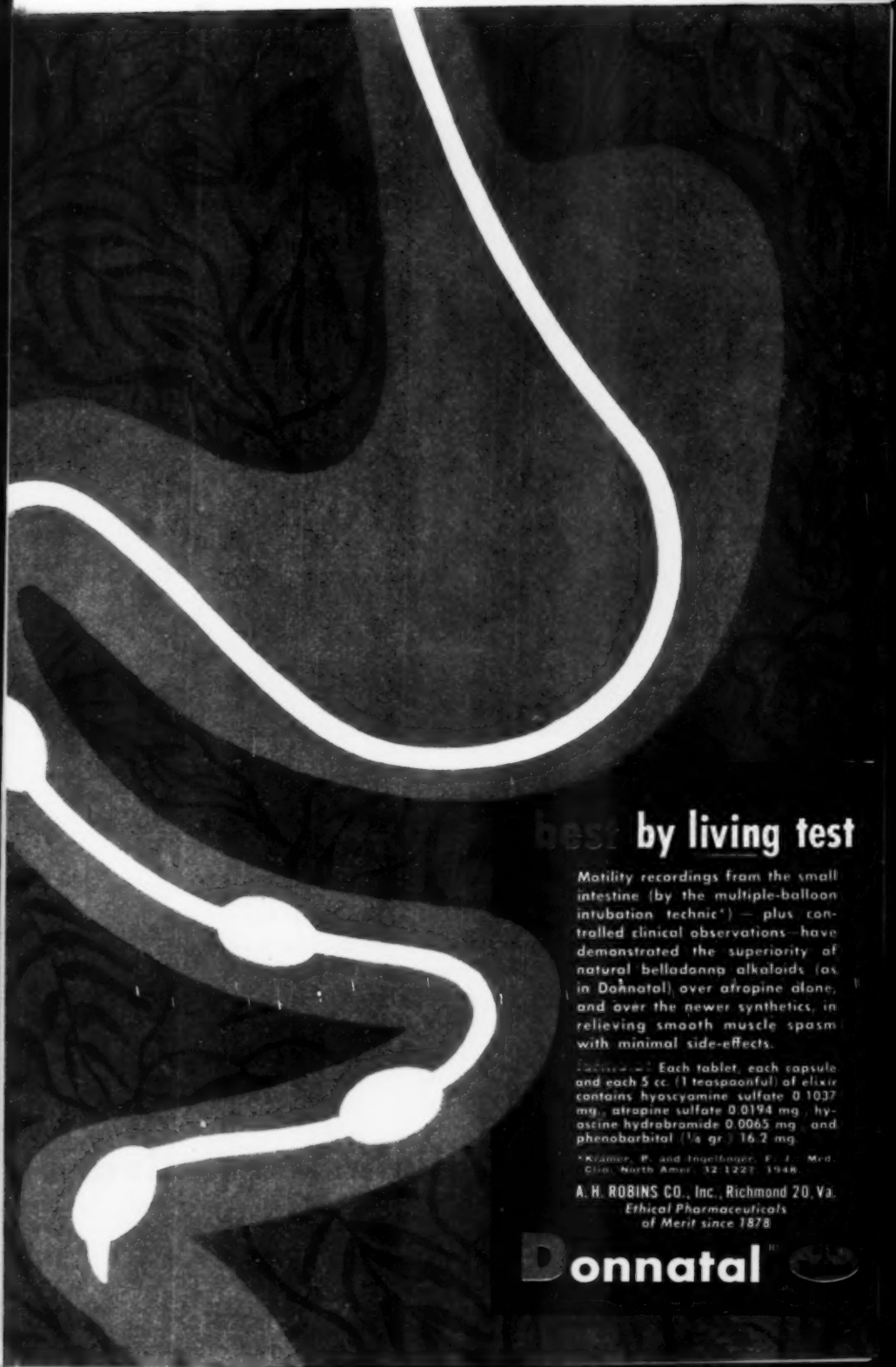

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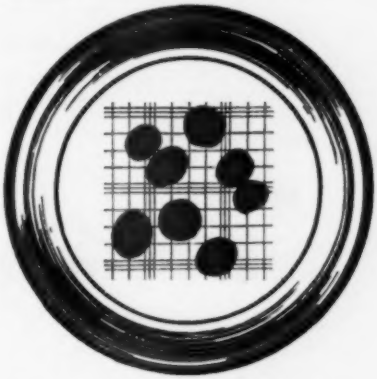

more than specific therapy...

may be needed to accelerate recovery in the common anemias.

In treating microcytic hypochromic anemia, particularly in the patient of reproductive age or when blood loss of any type is a conditioning factor, you will want to prescribe **not only iron but also all the elements known to be essential for the development and maturation of red blood cells.** "Bemotinic" provides all these factors.

Each capsule contains:		
Ferrous sulfate exsic. (3 gr.)	200.0	mg.
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Gastric mucosa (dried)	100.0	mg.
Desiccated liver substance, N.F.	100.0	mg.
Folic acid	0.67	mg.
Thiamine HCl (B_1)	10.0	mg.
Vitamin C (ascorbic acid)	50.0	mg.

In macrocytic hyperchromic anemias, the elements contained in "Bemotinic" will provide additional support to specific therapy, or may be used for maintenance once remission has been achieved. In many pernicious anemia patients there is need for iron because of a co-existent iron deficiency.

Suggested Dosage: One or two capsules (preferably taken after meals) three times daily, or as indicated.

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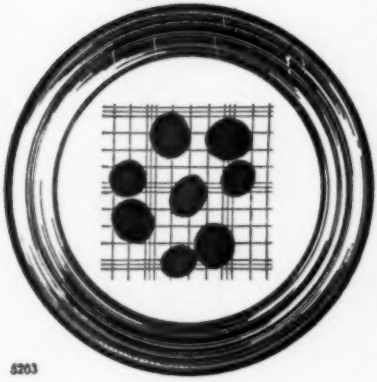

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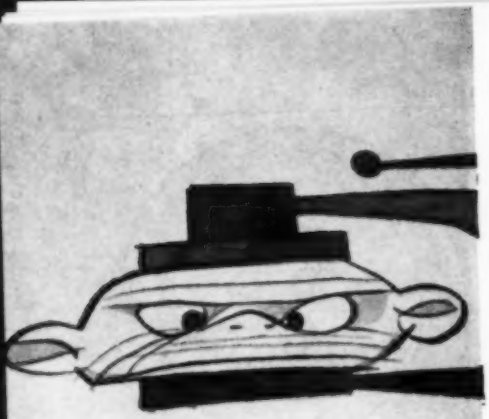

pressure

When

diet

work

worry

emotional disturbances

pressure, diet, work, worry,

emotional disturbances, visceroneurosis

cause ***Nervous Indigestion*** . . .

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BENTYL.....**10 mg.**
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DOSAGE—ADULTS: 2 capsules or 2 teaspoonfuls syrup 3 times daily, before or after meals. If necessary, repeat dose at bedtime.

IN INFANT COLIC: ½ to 1 teaspoonful syrup 3 times daily before feeding.[4]

visceroneurosis

Merrell
1828

New York • CINCINNATI • Toronto

1. Hock, C. W.: J. Med. Assn. Ga. 40:22, 1951 • 2. Hufford, A. R.: J. Mich. St. Med. Soc. 49:1308, 1950 • 3. Chamberlin, D. T.: Gastroenterology 17:224, 1951 • 4. Pakula, S. F.: To be published •

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when one must

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Supplied with sterile disposable 1 cc. cartridge syringe.

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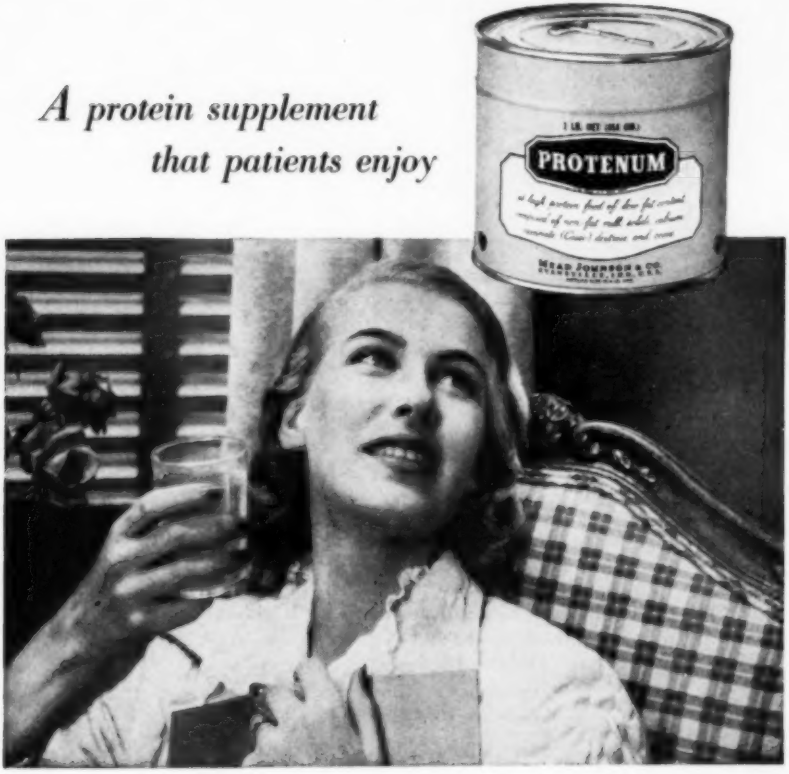

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Combines

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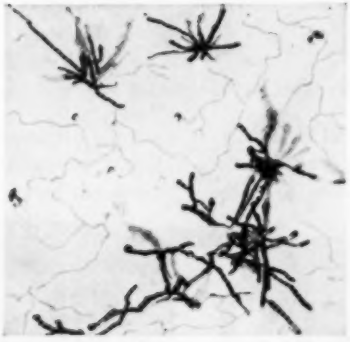
therapeutic

actions



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3. Check dehydration.
4. Help restore normal absorption of fluids and nutrients.
5. Promote development of formed, comfortably passed stools.

SUGGESTED DOSAGE

Four teaspoonfuls, three or four times daily before meals. Children, according to weight and response.

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And only KOLANTYL includes the important 4th factor

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Merrell
1828

DOSAGE: Two tablets every three hours as needed for relief. Mildly minted, Kolantyl tablets may be chewed or swallowed with ease.

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1. Meyer, K. et al. Am. J. Med. 5:462,1948. 2. Wang, K. J. and Grossman, M. I. Am. J. Phys. 155:476,1948. 3. Grace, W. J. Am. J. Med. Sc. 217:241,1949. 4. Hufford, A. R. Rev. of Gastroenterology, 18:568, 1951.

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REFERENCES:

1. Sturnick, M. I.; Riseman, J. E. F.; and Sagall, E. I.: Studies on the Action of Quinidine in Man: J. A. M. A. 121: 917 (March 20) 1943
2. Sagall, E. I.; Horn, C. D.; and Riseman, J. E. F.: Studies on the Action of Quinidine in Man: Arch. Int. Med. 71: 460 (April) 1943
3. Armbrust, Chas. A. Jr. and Levine, Samuel A.: Paroxysmal Ventricular Tachycardia: A Study of 107 Cases: Circulation, 1: 28-39 (Jan.) 1950
4. Bell, G. O.; Bradley, R. B.; and Hurxthal, L. M.: Paroxysmal Tachycardia, Experiences with Massive Doses of Quinidine Intravenously in a Refractory Case: Circulation, 1: 939 (April Part II) 1950

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1. Schaaf, R. S., Hurst, J. W., and Williams, C.: Med. Clin. North America (Mass. Gen. Hosp. No.) p. 1355 (Sept.) 1949

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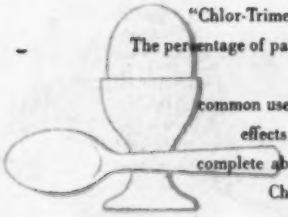

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†Silbert, N. E.: New England J. Med. *242*:931. 1950.

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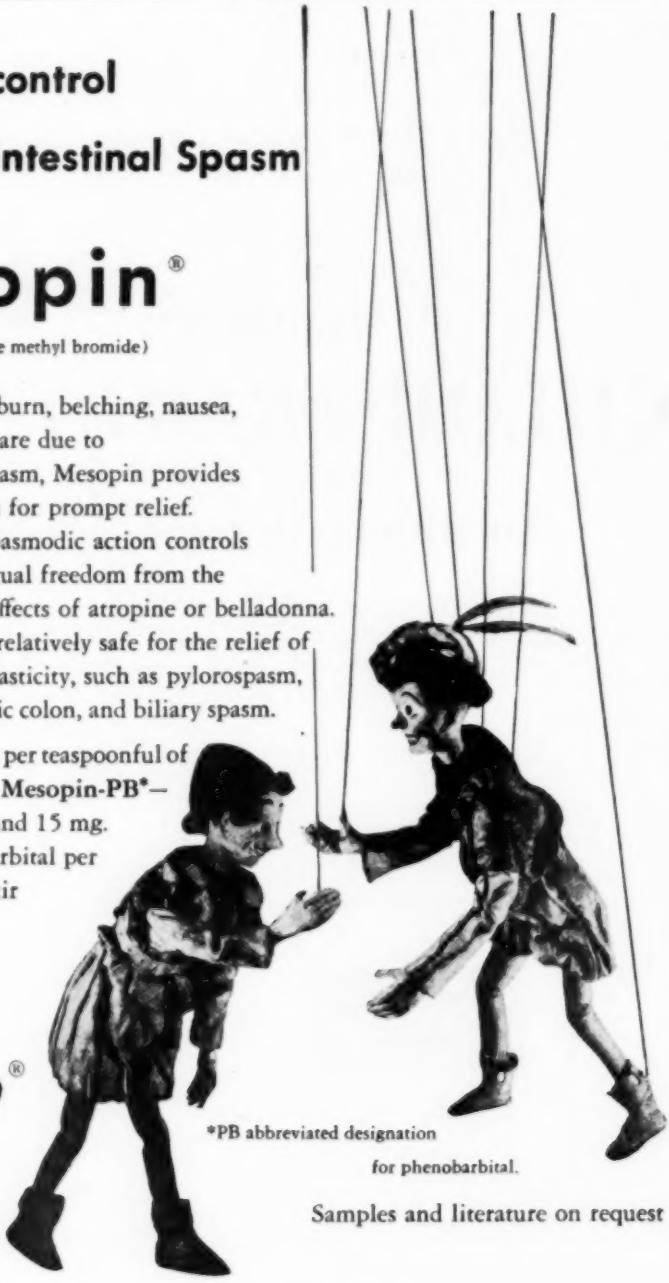

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•Spies, T. D.: Rehabilitation Through Better Nutrition, Philadelphia, W. B. Saunders Co., 1947. p. 62.

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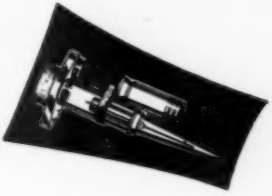

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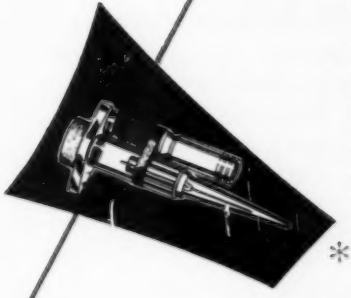

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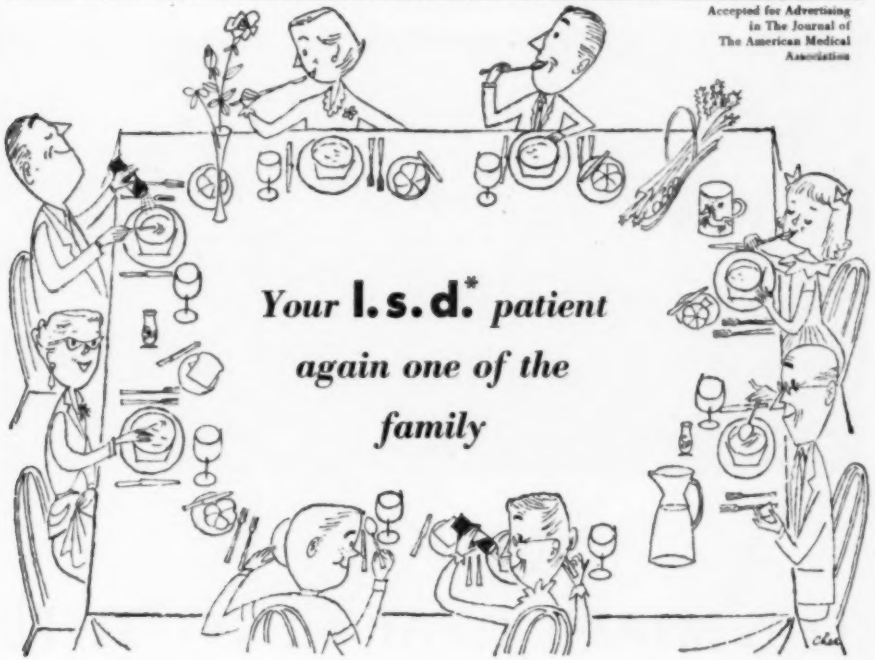

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1. Rimmerman, A.B., and Halpern, A.: A comparative study of sodium-free salt substitutes. Am. Pract. & Dig. Treatment 2:168 (February) 1951.
2. Fremont, R.E.; Rimmerman, A.B., and Shaftel, H.E.: The occurrence and management of the low potassium state with patients on the low sodium diet. Postgraduate Med. 9:—(September) 1951.

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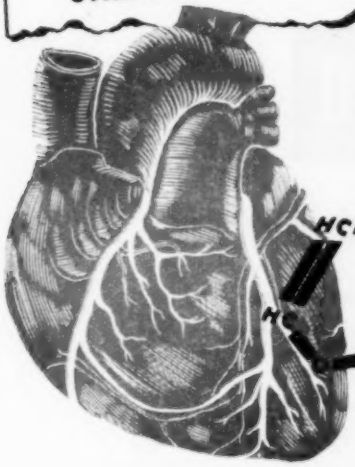

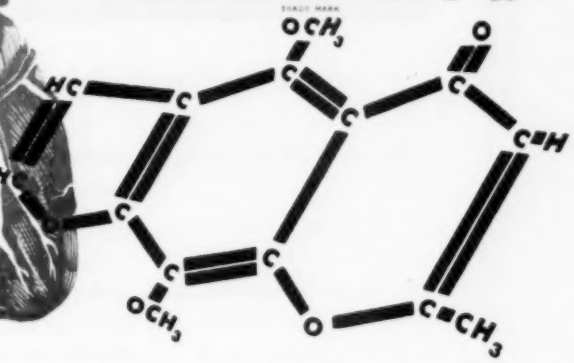

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1. Hutcheson, J. M.: Management of Cardiac Failure. *Virginia Med. Monthly*, 74:458, Oct., 1947.
2. Noth, P. H.: Pick's Disease: A Record of Eight Years' Treatment with Salyrgan, Ammonium Nitrate, and Abdominal Paracentesis. Proc. *Staff Meet. Mayo Clin.*, 12:513, Aug. 18, 1937.

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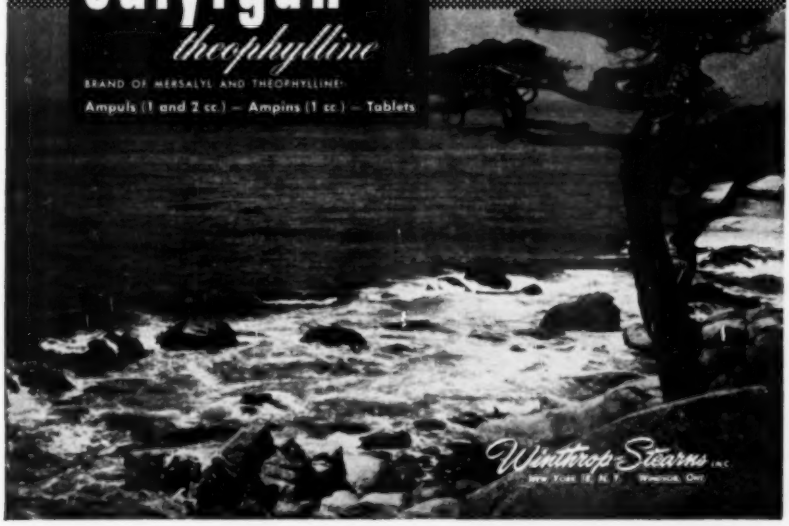

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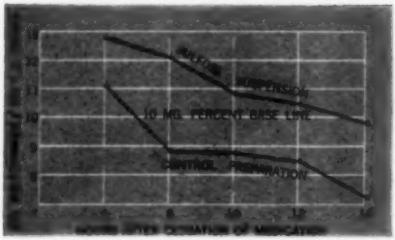

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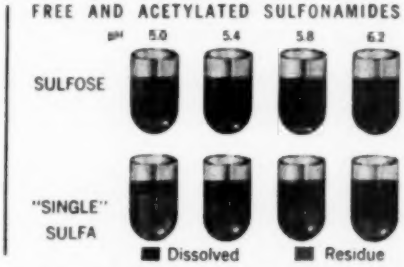

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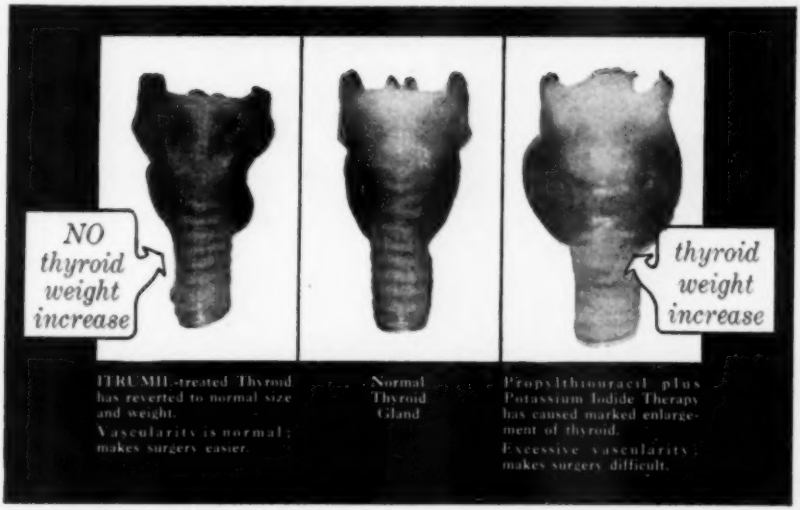
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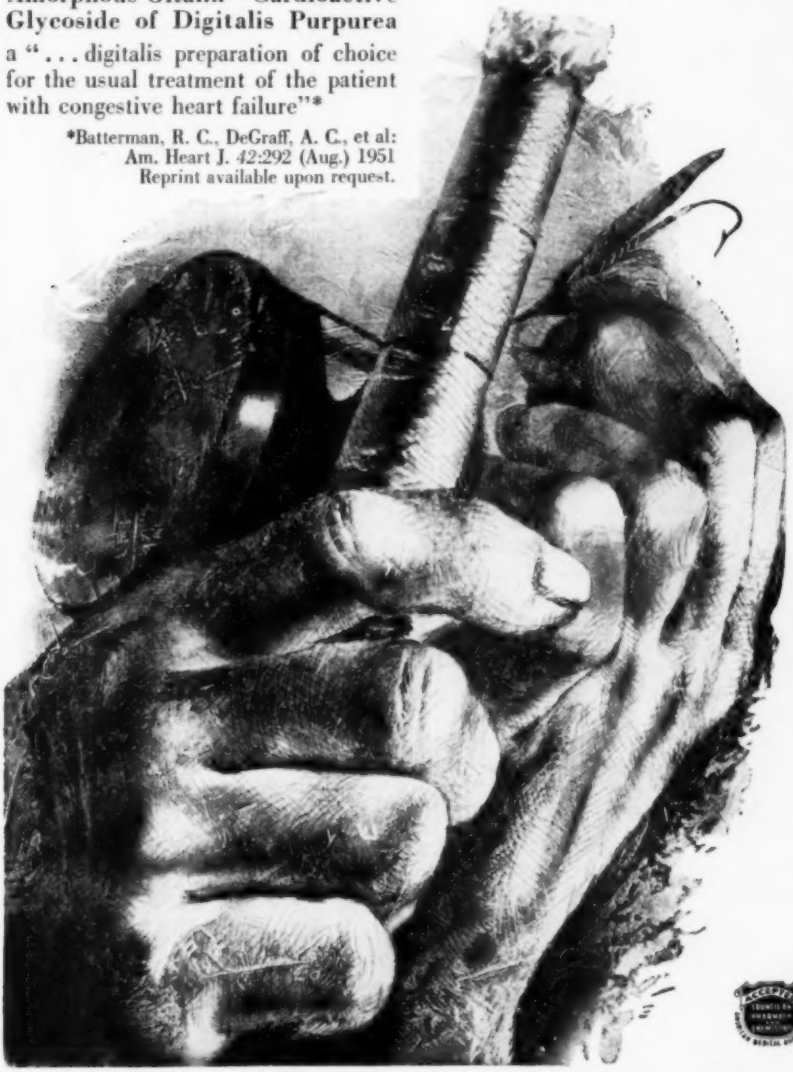

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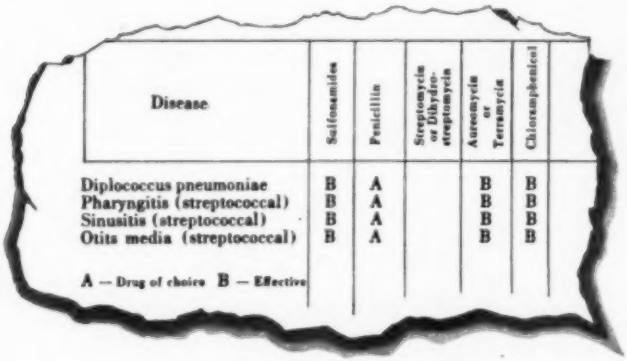

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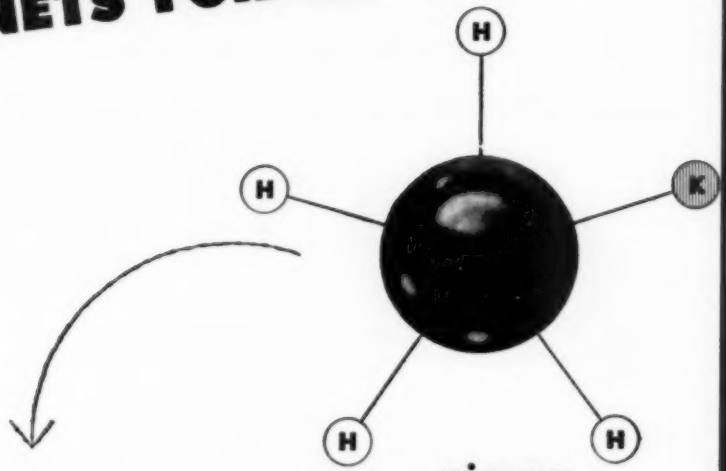

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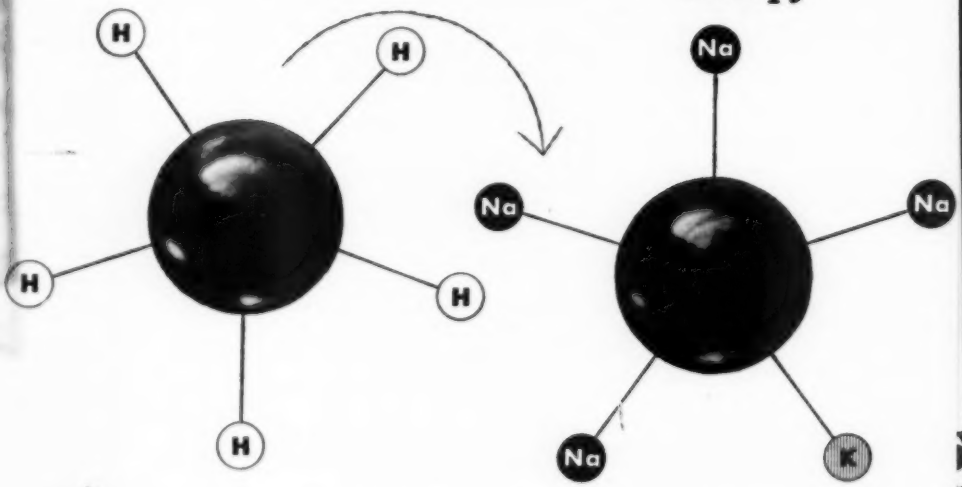

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2 Crossfield, H. C.: Cation Exchange Resins in the Control of Sodium Balance in Congestive Heart Failure. To be published.

3 Irwin, L., Berger, E. F., Rosenberg, B., and Jackenthal, R.: The Effect of a Cation Exchange Resin in Electrolyte Balance and Its Use in Edematous States, J. Clin. Investigation **28**:1403 (Nov.) 1949.

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5 Dock, W.: Sodium Depletion as a Therapeutic Procedure: The Value of Ion-Exchange Resins Withdrawing Sodium from the Body. Tr. A. Am. Physicians **59**:282, 1946.

6 Dock, W.: Congestive Heart Failure, J.A.M.A. **140**:1135 (Aug. 6) 1949.

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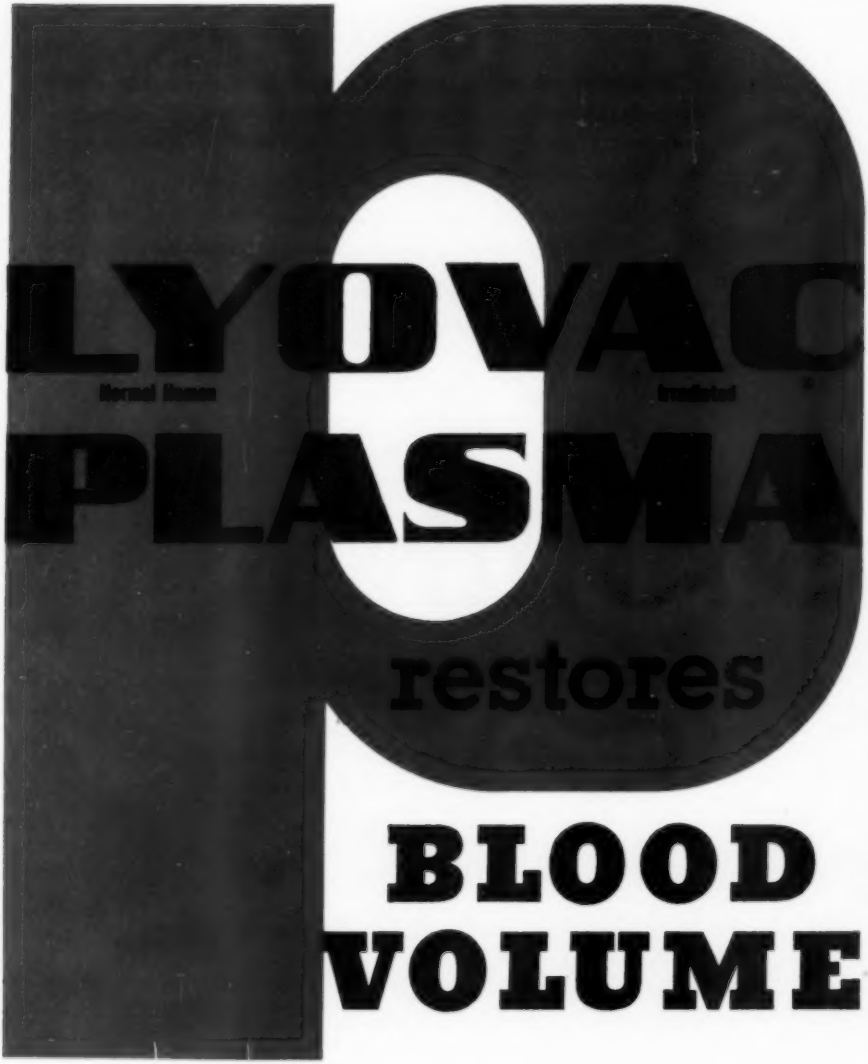

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ANNALS OF
INTERNAL MEDICINE

VOLUME 36 MARCH, 1952 NUMBER 3

THE EFFECT OF CORTONE AND ACTH ON THE HISTOPATHOLOGIC LESIONS OF RHEUMATOID ARTHRITIS *

By BERNARD M. NORCROSS, M.D., F.A.C.P., L. MAXWELL LOCKIE, M.D., F.A.C.P., *Buffalo, New York*, ANTHONY G. CONSTANTINE, M.D., *North Tonawanda, New York*, JOHN H. TALBOTT, M.D., F.A.C.P., and ROBERT H. STEIN, M.D., *Buffalo, New York*

THIS investigation was intended to demonstrate any effect of Cortone and ACTH upon the histopathologic lesions of rheumatoid arthritis. In 1945, Freund, Steiner and their associates [1, 2] described an inflammatory lesion of striated muscle in patients with rheumatoid arthritis. This lesion, consisting of a localized collection of lymphocytes, was widely distributed in the skeletal muscles, and was called "nodular polymyositis." The authors believed these lesions to be specific for rheumatoid arthritis, but other observers [3-5] have demonstrated the presence of similar changes in a variety of disease states and even in normal individuals. Two reports deserve special attention in this respect. Clawson and his associates [4] examined specimens of seven muscles from each of 450 routine autopsies, and compared the incidence of nodular and degenerative muscle lesions to the occurrence of these lesions in the deltoid muscle of 44 patients with rheumatoid arthritis. They determined that the inflammatory lesions were commonly present in patients with rheumatoid arthritis and, to a lesser extent, in the autopsy series. Bunim, Sokoloff and associates [6, 7] studied serial sections of skeletal muscle in 202 patients with rheumatoid arthritis and with other diseases (both rheumatic and nonrheumatic) and in normal individuals. Typical muscle lesions were present in 56 per cent of patients with rheu-

* Received for publication June 7, 1951.
From the University of Buffalo School of Medicine and the Buffalo General Hospital, Buffalo, New York.
This study was aided by a grant from the Weed Foundation, Buffalo, New York.
Portions of this paper were given at the annual meeting of the American Rheumatism Association, June 23, 1950, San Francisco, and also at the Western New York Regional Meeting of the American College of Physicians, October 14, 1950, Rochester, New York.

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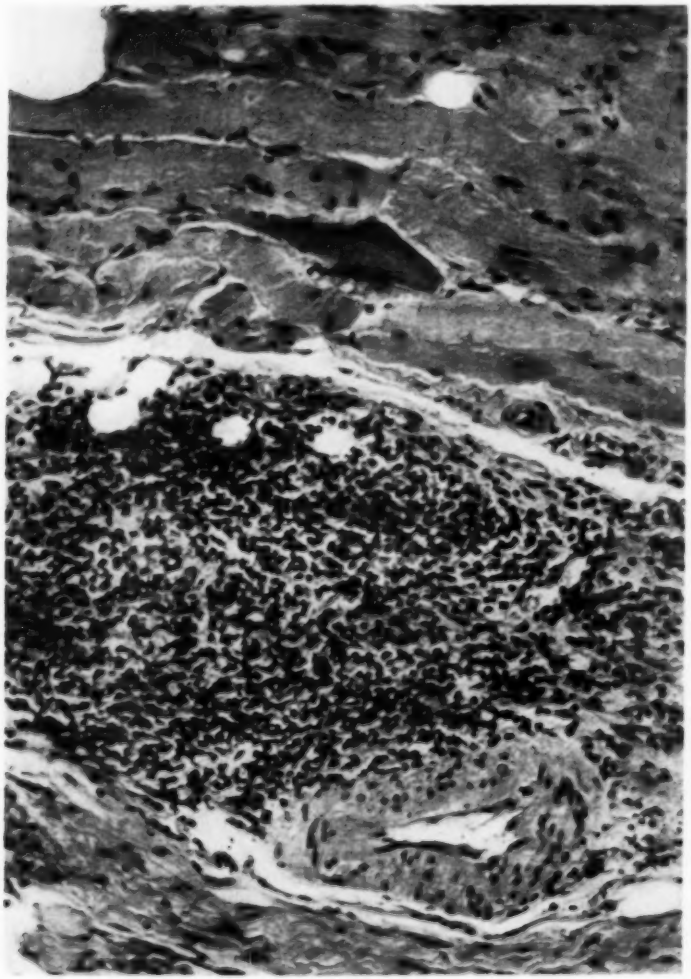

FIG. 1. P. G., female, age 50 years, rheumatoid arthritis, Stage II, Class IV, duration three years. Large inflammatory nodule obtained from the right deltoid muscle prior to Cortone therapy. This lesion was visible grossly. The sarcolemmal nuclei are prominent, and a vacuole is observed in a muscle fiber. Other sections demonstrate marked areas of focal degeneration of muscle fibers. (× 240.)

FIG. 2. P. G., section obtained from the right deltoid after three weeks of Cortone therapy. No inflammatory or degenerative lesions were present in the muscle sections. (× 240.)

matoid arthritis. Similar lesions were present in the other disease states and in the normal individuals, but to a lesser extent.

Since our intention was to demonstrate only the probable effect of Cortone and ACTH upon the muscle lesions, the question of specificity of these lesions for rheumatoid arthritis was not involved. Furthermore, the occurrence of similar lesions in other "collagenous diseases" adds to the interest of such a study.

Procedure

This group of 30 patients included 27 with peripheral rheumatoid arthritis, two patients with rheumatoid spondylitis and one patient with rheumatoid arthritis associated with psoriasis. Muscle biopsies were performed prior to therapy, and were repeated at intervals during therapy if the initial sections demonstrated significant findings. Since the frequency of muscle lesions is somewhat variable, the same surgeon obtained the specimens, using similar atraumatic technic. Several muscles were examined (the deltoid was the most frequent), and serial sections were carefully examined by the same pathologist.

The muscle specimens were studied for both the inflammatory nodules and the degenerative changes in the muscle fibers. We believe that the degenerative changes have some significance, because there is a close correlation with the presence of the inflammatory lesions. An attempt was made to grade both lesions for severity to aid in the evaluation of any treatment effect. The inflammatory nodule was classified in the following manner. Grade I was a single collection of about 50 lymphocytes; Grade II consisted of two to five such smaller nodules (50 cells), or one large nodule; and Grade III was represented by more than one large nodule or more than five smaller nodules. The degenerative lesion was also graded I to III on the degree of the following changes: localized or diffuse atrophy of the muscle fibers, increase in the size and number of the sarcolemmal nuclei, loss of striations and hydropic swelling of the fibers. Only those patients who demonstrated both inflammatory and degenerative muscle lesions of at least Grade II severity were used to evaluate the effect of hormonal treatment.

Since the subcutaneous nodule is generally considered the most characteristic pathologic lesion of rheumatoid arthritis, these lesions were carefully observed in 12 patients. In three patients, nodules of the same apparent stage of development were removed before and during hormonal therapy. All nodules appeared typical prior to treatment. The central necrotic zone, the surrounding layer of large mononuclear cells in palisade formation and the outer zone of connective tissue with marked round cell infiltration could be demonstrated in all instances.

Biopsy of the synovial membrane was obtained in two patients before and during hormone therapy. In each case, the knee joint was the site employed.

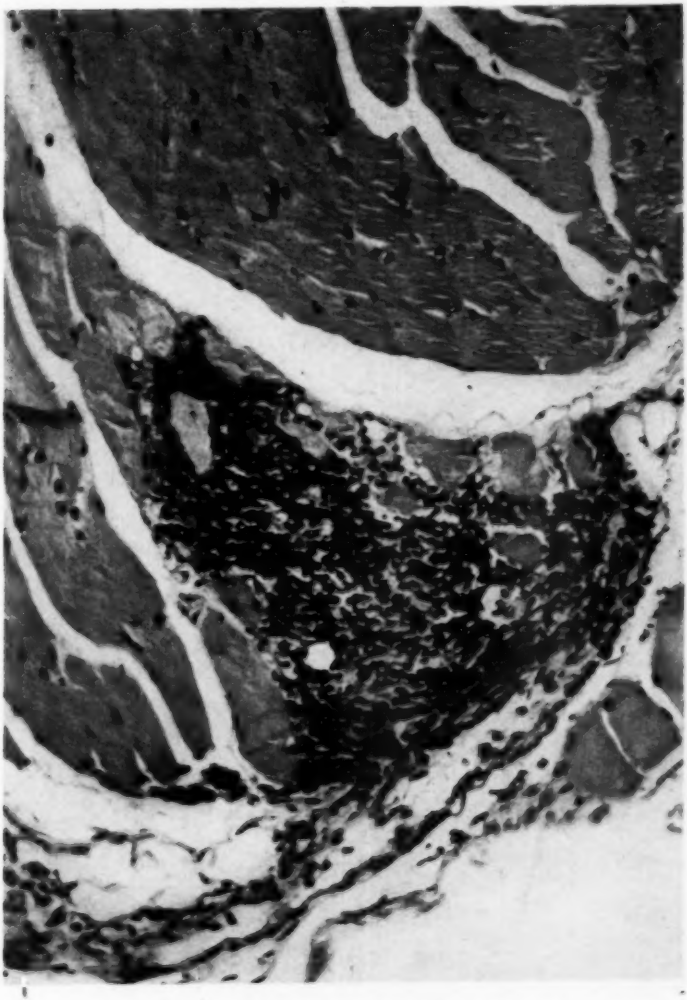

FIG. 3. A. N., female, age 55 years, rheumatoid arthritis, Stage I, Class II, duration seven months. Large inflammatory nodule obtained from left deltoid muscle. This lesion is both perimysial and endomysial in location. Other sections demonstrated a moderate degree of diffuse atrophy of muscle fibers. (× 240.)

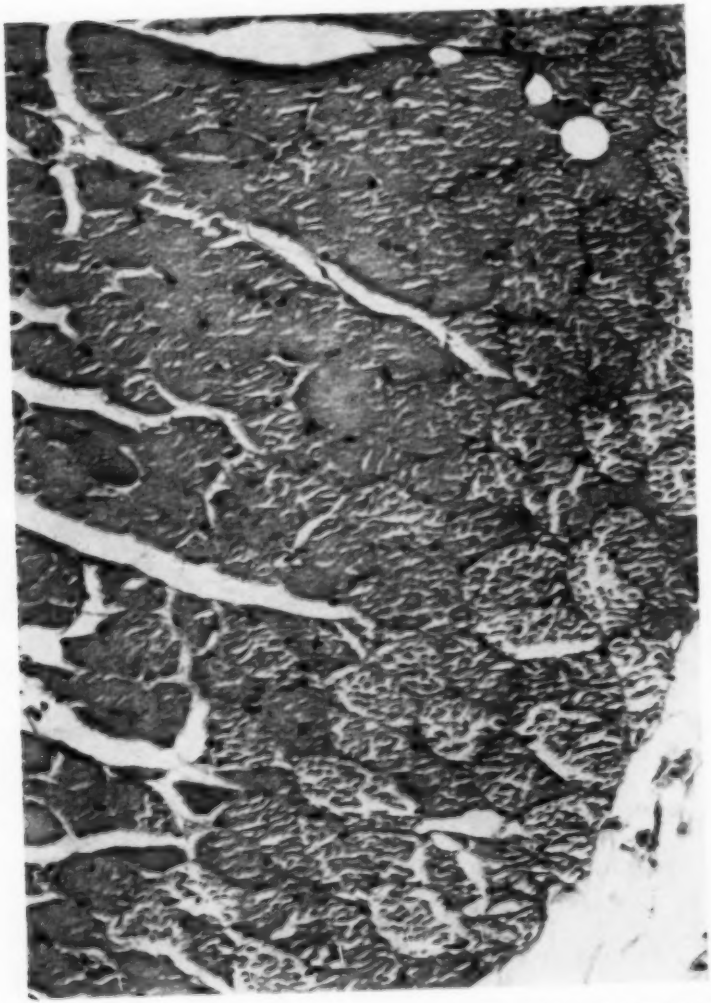

FIG. 4. A. N., section obtained from the left deltoid muscle after 18 days of ACTH therapy. No abnormalities were demonstrated. (× 240.)

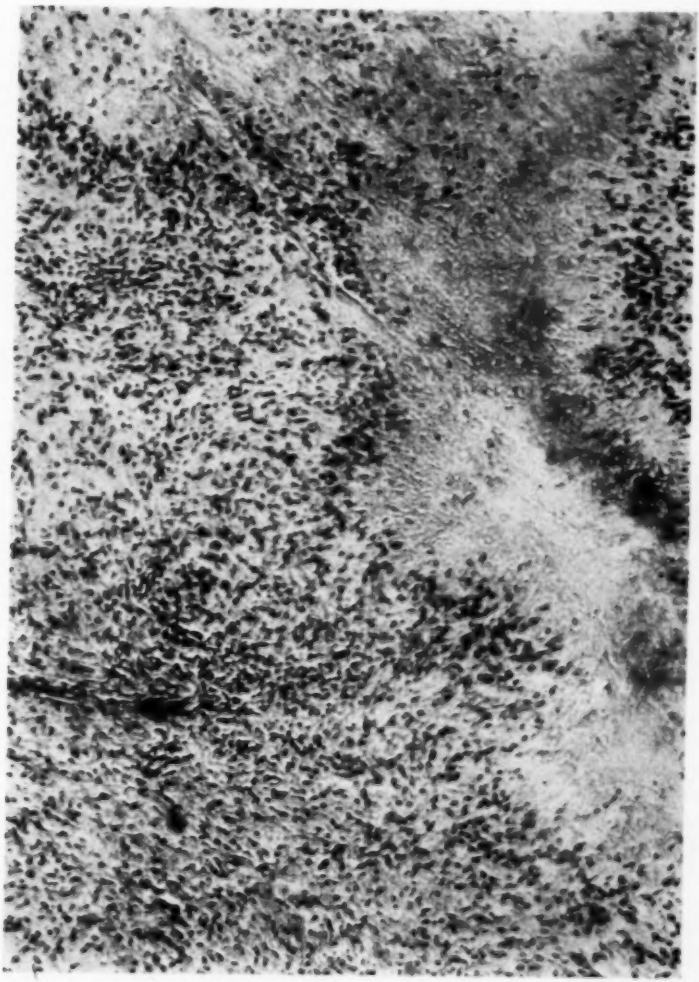

FIG. 5. H. C., male, age 45 years, rheumatoid arthritis, Stage III, Class III, duration 13 years. Subcutaneous rheumatoid nodule removed from right forearm prior to Cortone therapy. Characteristic appearance of central necrotic zone, surrounding palisade layer of larger mononuclear cells, and outer zone of collagen fibers with marked round cell infiltration. (× 100.)

Results

Both the inflammatory and the degenerative lesions were present in the muscle specimens in 18 of the 30 patients. However, only 11 patients were considered to have significant (Grade II or Grade III) changes to evaluate the effect of the hormonal therapy. In eight of the 11 patients (72.7 per cent), there appeared to be definite improvement in both lesions produced by Cortone or ACTH administration. The inflammatory nodules disappeared in five and were improved in the other three patients. Degenerative muscle changes improved in the eight patients, but to a lesser extent than the inflammatory ones. The more rapid and complete response of the inflammatory lesions would be reasonable to expect during short periods of treatment.

Subcutaneous rheumatoid nodules were altered considerably in the 12 patients during the period of hormone administration. Many small nodules practically disappeared, while the large nodules became smaller, less painful and less inflammatory in appearance. There was a definite histologic change in two of the three patients from whom comparable nodules were removed before and during therapy. The central necrotic zone became poorly defined; the palisade layer of mononuclear cells practically disappeared; the outer zone of fibrous tissue appeared more dense (or hyalinized), and the round cell infiltration was markedly diminished. However, this alteration may represent a stage in the evolution of these lesions rather than a specific effect of the hormones. Other observers [9, 10] have reported similar clinical changes in the size and appearance of the subcutaneous nodules during therapy with Cortone and ACTH.

A marked reduction of synovial inflammation occurred in both patients in whom articular biopsies were performed before and during hormone therapy. Prior to therapy, the synovia was congested and edematous, but after three weeks of hormone treatment it appeared normal to inspection. The gross improvement was confirmed by histologic examination. There was a marked reduction of cellular reaction, with almost an absence of lymphocytes and plasma cells, and a marked decrease in vascularity and edema. This improvement has been noted by Hench [10] and Bauer.[11]

No difficulty in healing of the incisions was noted in this group, even though multiple procedures were performed in many patients. However, delay in wound healing has been reported.[12, 13] We were unable to correlate the presence or severity of nodular polymyositis or subcutaneous nodules with the extent, duration, activity or the therapeutic response of the rheumatoid process.

Summary

Cortone and ACTH produced significant alterations in the histopathologic lesions of patients with rheumatoid arthritis. Definite improvement was observed in the inflammatory nodules found in striated muscles and

FIG. 6. H. C., subcutaneous rheumatoid nodule of same apparent stage of development as lesion in figure 5, removed after two weeks of Cortone therapy. Considerable change in the appearance of the lesion is demonstrable. The central necrotic zone is poorly defined, the collagen fibers appear more hyalinized, the palisade layer of cells has disappeared, and the round cell infiltration is markedly diminished. (× 100.)

FIG. 7. R. C., female, age 41 years, rheumatoid arthritis, Stage IV, Class IV, duration 20 years. Biopsy of left deltoid muscle prior to Cortone therapy illustrates well advanced degenerative changes. There is a marked variation in thickness of the muscle fibers and marked nuclear proliferation in all sections. Many fibers are atrophic, and areas of actual disintegration are noted. Seven nodular infiltrates were observed in the same specimen.

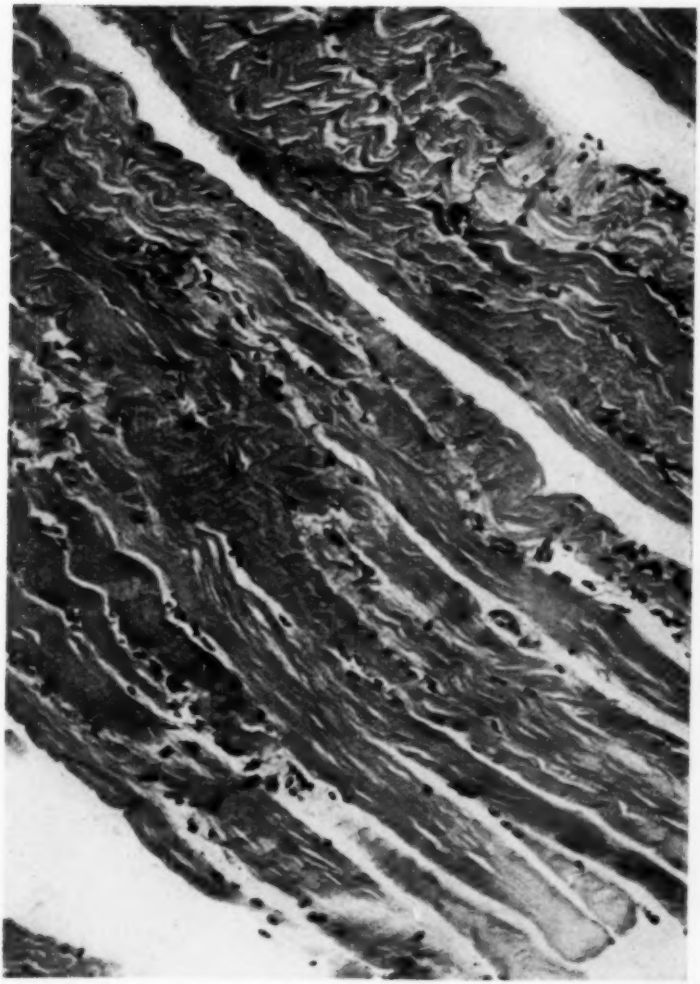

FIG. 8. R. C., specimen of left deltoid muscle obtained after 60 days of Cortone therapy. No evidence of degenerative or inflammatory lesions was observed in multiple sections. (× 240.)

FIG. 9. H. J., female, age 53 years, rheumatoid arthritis, Stage I, Class III, duration six months. Synovial membrane obtained by biopsy of the right knee prior to ACTH therapy. Characteristic changes of active synovitis are seen; also marked edema, hyperemia, papillary hyperplasia, fibrinoid exudate and marked infiltration by lymphocytes and plasma cells. (× 200.)

FIG. 10. H. J., synovial membrane of the right knee after 16 days of ACTH therapy. There is marked improvement of the inflammatory process. Only minimal edema, hyperemia and focal lymphocytic infiltration are seen. The synovial surface is smooth and no exudate is present. (× 200.)

also in the inflammatory changes of the synovial membrane during hormone administration. Clinical improvement of subcutaneous nodules was noted, but further histologic evidence is necessary before final conclusions are warranted. No delay occurred in the clinical healing of the surgical wounds of this group of patients during Cortone or ACTH administration.

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BENIGN AND PATHOLOGIC ALBUMINURIA: A STUDY OF 600 HOSPITALIZED CASES *

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Introduction

Albuminuria discovered in apparently normal individuals without prior evidence of renal disease always poses a perplexing problem. It is essential that an accurate diagnosis be made promptly for many reasons, including insurability and military availability, and to allay anxiety or to institute proper treatment. Frequently, these individuals are subjected to exhaustive studies of renal function and urography, with results not commensurate with the effort involved. This is often due to lack of a systematic approach to the problem. The clinical features of the various types of albuminuria permit differential diagnosis in most instances without an unnecessarily cumbersome approach. To determine availability for military service, a rapid, practical procedure is particularly necessary for the screening of large groups of cases detected at Army induction stations. Sufficient accuracy is required to exclude induction of individuals with significant or progressive renal disease, and, conversely, to avoid unnecessary rejection of individuals with benign albuminuria.

To fulfill these criteria, a standard procedure (SOP) was devised [1] (described below) to include Addis count, concentration test and a series of timed urine collections over a 24 hour period under conditions designed to elicit albuminuria. This report is based upon the study of 600 consecutive cases referred for brief hospital study by Army induction stations after the finding of albumin in at least three specimens of urine during examination.

Benign Albuminuria

Albuminuria without manifest renal disease is recognized as a frequent condition. Most group studies have been compiled incident to military induction and college physical examinations.[2, 3] Incidences of 11.6 per cent [4] to 16 per cent [5] have been reported in large groups. The figures of Diehl and McKinlay [6] (5.3 per cent in 20,000 college freshmen), Murphy [7] (3 per cent in 9,990 Navy applicants), Blatherwick [8] (3.3 per cent in 15,000 Metropolitan Life employees), and Wolman [9] (1.9 per cent in 22,000 inductees) are probably more representative. A compilation made by us of 75,000 cases in the literature in the age group similar to that of inductees gave an incidence of albuminuria of 3.3 per cent.

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The term "benign albuminuria" is a general clinical designation for all varieties of albuminuria not due to serious or progressive organic disease. It probably has no physiologic significance, and it includes several distinct varieties. The terms intermittent, cyclic, transient, lordotic and orthostatic albuminuria are not synonymous, although often used interchangeably. The following varieties of benign albuminuria are recognized.

A. *Transitory Albuminuria.* This variety, which represents about 75 per cent of cases in all large-scale examinations, denotes albuminuria which cannot be regularly duplicated, even on multiple reëxaminations over several days. Such findings must represent a transient phenomenon, either occurring only under conditions incident to examination, or cyclic over longer periods.

Transient albuminuria may be caused by urinary contamination with seminal or prostatic secretion, or by acute lower urinary tract infection (urethritis, prostatitis). Toxic conditions, systemic infection and hyperthermy may cause "febrile albuminuria."[10] The frequency in routine examinations of albuminuria due to such fortuitous and exceptional conditions, however, must be slight.

Intense and prolonged physical activity and severe emotional strain produce fleeting albuminuria.[13, 14] Arhonheim[14] noted albuminuria in Air Force personnel following the emotional tension of aerial combat missions, and related its occurrence to the general psychiatric pattern of the individual, indicating that predisposed individuals under extreme emotional tension developed transient albuminuria. Albuminuria has been reported following head injuries, subarachnoid hemorrhage[15] and experimental puncture of the brain stem. Albumin and abnormalities of the urinary sediment may follow encephalography.[16] Such effects may be mediated by endocrine or neurogenic channels. Changes in renal function may follow emotional stimuli.[17] Decreased renal blood flow and simultaneously increased limb volume have been reported[18] after cerebral cortical stimulation. Such changes in renal function are independent of the systemic blood pressure and appear due to selective renal vasoconstriction.[19, 20] Selye[21] considers the albuminuria of situations of stress as part of the adaptation syndrome.

B. *Postural Albuminuria.* Orthostatic, lordotic, postural, variable and juvenile albuminuria are terms used interchangeably in the literature to describe that form of benign albuminuria which can be produced regularly by certain bodily postures. These are the "conditioned proteinurias" of Addis.[22, 23] A voluminous literature has developed about these abnormalities. Clinical observations suggest that these abnormalities rarely develop into severe organic renal disease. Orthostatic albuminuria has been reported by Derow[24] in several cases of glomerular nephritis in the convalescent state.

The lordotic position, either erect or recumbent, is often considered the sole provocative factor causing albuminuria.[25, 26] In normal individuals,

prolonged assumption of lordotic position, as after application of body casts (Lewison, Friedman and Read [27]), does not cause albuminuria. Most observers believe that this abnormality is due to some underlying congenital defect of renal structure which, under certain conditions of posture or activity, predisposes to albuminuria.[22] The provocative conditions presumably cause disturbance of renal circulation and hence albuminuria. It may occur in the lordotic position, after assumption of the erect position, prolonged standing or physical activity. Rolleston [28] described hypostatic albuminuria following recumbency. Cases have been reported associated with enlargement of abdominal viscera presumably due to pressure upon the renal circulation. The variable albuminuria of pregnancy without renal disease or toxemia may be of similar origin.

Pathologic Albuminuria

A. *Persistent Albuminuria.* This is characterized by positive reactions for albumin at all times, regardless of posture or activity, and is generally considered presumptive evidence of renal disease. These cases with albuminuria present in all specimens may give no history, clinical features, abnormalities of urinary sediment or other evidence of Bright's disease.

B. *Chronic Glomerulonephritis.* In this disease, persistent albuminuria is associated with abnormalities of the urinary sediment, particularly red cells. History and abnormalities on physical examination or renal function tests are of aid in the diagnosis.

C. *Chronic Pyelonephritis.* In this disease, albuminuria may be persistent, intermittent or absent. Pyuria also may be intermittent, and occasionally hematuria may occur. Exclusion of disease of the lower genitourinary tract and positive urine culture for *Escherichia coli*, hemolytic streptococcus or staphylococcus are valuable diagnostic features. History is of positive value only. Persistent albuminuria and cylindruria occur in the advanced stage, when they may be associated with hypertension and impaired renal function. At that stage, differentiation from glomerular nephritis may be difficult. Differentiation of primary from secondary pyelonephritis, associated with calculus, urinary obstruction or congenital renal disease, can be made only by urologic study.

D. *Miscellaneous Urinary Tract Infections.* Infections of the lower urinary tract are rarely associated with albuminuria of any degree or persistency (in the centrifuged specimen). Pyuria is present and infection is demonstrable on routine urologic survey.

Pathologic Physiology of Albuminuria

Minor changes in renal function may induce albuminuria. White [29] considers the albuminuria following exercise as due to renal vasoconstriction. He noted that effective renal plasma flow (PAH clearance), on standing as

compared to recumbency, is diminished about 20 per cent and glomerular filtration 8 per cent. Following severe exercise, these are reduced to one-half or less of the recumbent level. Albumin does not appear during the stage of renal vasoconstriction but in the first urine specimens thereafter. Presumably, any stress, reflex, cold, pain, psychogenic shock, etc., may produce albuminuria through renal vasoconstriction. This may be the basis for so-called physiologic albuminuria.

The mechanism of the loss of serum protein into the urine has been the subject of controversy for many years.[22, 23] This was first considered due solely to increase in glomerular permeability, as in the damaged glomeruli of nephritis. The demonstration that protein normally occurs in small amounts in the filtrate of amphibians (Richards [30]) and mammals (Walker and Oliver [31]) has caused reconsideration of the entire subject. Addis [22] presents considerable evidence indicating the importance of tubular function in relation to albuminuria in nephritis.

Transient depression of tubular function with albuminuria has been produced by Dock [32] by chilled plasma perfusion of the kidney. Addis considers that intermittent albuminuria denotes an actual, albeit transient, degenerative renal tubular lesion. He believes that in rare instances it denotes a congenital defect of the tubular transport system, akin to renal glycosuria.

The effect of the lordotic position in producing albuminuria is considered (Jehle [25]) due to compression of the renal vein. The concept of congenital renal anomalies subject to disturbances in renal hemodynamics with postural changes is the most plausible theory for postural albuminuria (Addis [23]). Diminished diodrast excretion on the involved side has been reported by Rytand [33] in cases of unilateral albuminuria. This subject has recently been reviewed in detail by Bull.[26] Compiling all 18 catheterized cases in the literature, including his own, he points out that the albuminuria was unilateral in 10 instances and bilateral in 8. In his series of postural albuminuria he found no evidence of neurocirculatory asthenia, and blood pressure, pulse pressure and cold pressor reactions were normal. He observed in the erect lordotic position a marked reduction in urinary secretion, as well as reductions in renal plasma flow (PAH) and glomerular filtration rates. These variations, however, are of about the same order as those reported by White [29] for normals, the only differences being that Bull compared the erect lordotic with the recumbent.

Bull considers the oliguria and marked reduction in urea and chloride clearance as indicative of increased reabsorption of filtrate. In conjunction with the increased circulation time and elevated inferior caval pressure (catheter studies) noted in the erect lordotic position, he considers the changes in renal function as similar to those in cardiac failure. From these studies, Bull has developed the interesting hypothesis that in predisposed individuals (with an inferior cava deeply embedded in the posterior surface

of the liver) the lordotic position produces caval compression between the anteriorly rotated liver and the spine. Such caval compression would cause bilateral renal venous obstruction and albuminuria. This theory, however, does not adequately explain unilateral albuminuria. Our own observations (subsequently cited) dispute the rôle of lordosis as the only postural stress that may induce albuminuria. Considering the technical difficulties of the clearance methods, the significance of these results in small groups cannot be appraised until confirmed on a larger scale. The only justifiable conclusions at present are that postural albuminurias are of multiple etiology, representing various structural abnormalities of the kidneys, renal vessels and perhaps vena cava. Under conditions of strain, imposed by various positions, interference with renal circulation and function results in albuminuria.

Differential Diagnosis of Albuminuria

Certain pitfalls must be recognized in the differential diagnosis of various types of albuminuria, since sources of error exist in both directions. Albuminuria in the healing stage of glomerulonephritis may be inconstant and appreciably increased by the erect posture and activity, as well as by a high protein diet (Berglund [34]). Derow [24] reported postural albuminuria persisting for some months in four cases of healing glomerulonephritis and two cases of healing pyelonephritis. In some instances of postural albuminuria, Addis sediment counts above the accepted normal limits may cause confusion. By attention to a few precautions, however, the diagnosis may be made with assurance in most instances.

In latent glomerulonephritis, albuminuria may be reduced to a mere trace, which may no longer be demonstrated in very dilute or alkaline urines. Dilute urine specimens with specific gravity below 1.016, therefore, are not reliable when negative. It is desirable to insure fluid restriction prior to and during periods of collection. Presumably the factor of urinary concentration with diluting out of protein explains the so-called seasonal variation of benign albuminuria, with the highest incidence during the summer months, when even casual urine specimens are concentrated.

The amount of albuminuria may be a rough guide to diagnosis. In most cases of benign albuminuria, proteinuria is below 100 mg. per cent (i.e., 2 plus with the quantitative turbidity procedure), while the mean values in glomerulonephritis usually exceed 200 to 300 mg. per cent (3 plus or more). This is not invariable, and cases of benign albuminuria with higher concentrations are occasionally noted. Proteinuria from any cause may be increased by activity or by the erect or lordotic position. In general, proteinuria in nephritis is persistent in all specimens, whereas intermittence is characteristic of benign albuminuria. In the earlier stages of renal vascular disease and in urinary tract infections, albuminuria may be intermittent or occasional, and with postural effects (Derow [24]). In advanced arteriolar nephrosclerosis, albuminuria is persistent. Age differences and the coexist-

ence of vascular hypertension or its sequelae render this a simple differential problem. To repeat: A mild, intermittent albuminuria in young individuals, absent on recumbency and increased by erect or lordotic posture, or activity, with normal urinary sediment and without other evidence of renal vascular disease, may be accepted as a benign abnormality.

Persistent albuminuria in apparently normal individuals without renal disease and with normal urinary sediment poses a more difficult problem. It is generally assumed that such cases denote latent organic renal disease. In accordance with military directives, such cases are considered unfit for military duty. The definition of "persistent" is not clearly defined, since a series of daily positive specimens in the erect posture may be disqualifying, although recumbent specimens if taken would be negative. Albuminuria in cardiac failure rarely presents any serious diagnostic problem.

The basic feature of serious renal disease is constant excretion of albumin, usually with formed elements (red cells, white cells, epithelial cells and casts), depending upon the nature of the process. These are best demonstrated in concentrated urines by the Addis quantitative technic. It is generally assumed that such abnormal elements are absent in benign albuminuria. As previously pointed out, this is only approximately correct. Addis calls attention to the occurrence of increase of casts and epithelial cells (often included as white cells) in specimens obtained under strain conditions in postural albuminuria. The number of cells and casts, however, is less than in organic renal disease. These findings have been confirmed by Rytand [22] and others. Bull [26] showed a direct relationship between the degree of albuminuria induced by posture and the excretion of formed elements, with Addis counts up to 0.5 million red blood cells, 2.0 million white blood cells and 200,000 casts. Such findings must be recognized as usual in these cases.

Method of Study

The clinical material consisted of 600 draft examinees referred to this hospital because albuminuria was noted in three specimens on two days. It is estimated that, in 75 per cent of the cases, transient albuminuria noted once was not reduplicated, and such patients were not referred for study. Ages varied from 17 to a maximum of 32. After the initial draft and reëxamination of the 21 to 25 age group (many previously rejected during World War II), examinees fell largely into the 17 to 21 age group.

Initial urines were collected at various times of day at induction stations, depending upon the examination schedule. Many cases of orthostatic albuminuria were undoubtedly missed because of this timing. Urines were examined for albumin by the turbidimetric method. Cases revealing albuminuria were reëxamined the same day. If one negative specimen was found on reëxamination and no changes in sediment were present, the case was considered without pathologic significance.

Following hospitalization, all cases were studied as follows:

Patients reported to the hospital in the afternoon and the first urine specimen was taken at 8 P.M., at which time they were put to bed and fluids were restricted until morning. The second specimen was a 10 hour pooled urine from 8 P.M. to 6 A.M. for the Addis count. Fluid restriction also made this specimen a mild concentration test. Patient had breakfast (one glass of juice or milk while still in bed between 7 A.M. and 8 A.M.) and then assumed a lordotic position by means of pillows under the lumbar spine. This was maintained for two hours, and the third specimen was then collected. (Subsequently the procedure was modified to eliminate the lordotic posture, but the second recumbent specimen was retained as a check on the night collection.) Patient was then permitted ward activity. After lunch, a fourth specimen was collected. In some cases, additional specimens were

TABLE I

Differential Diagnosis of Albuminuria

	Albuminuria			Sediment (Addis Count)		
	Recumbent	Erect	Lordotic	WBC	RBC	Casts
Transitory	0	inconstant	0	0	0	0
Orthostatic	0	+*	0	0	0	0
Lordotic	0	0	+	0	0	0
Combined (lordotic-orthostatic)	0	+*	+	0	0	0
Persistent	+	+	+	0	0	0
Glomerulonephritis	+	+	+	±	++	+
Pyelonephritis†	(variable, often persistent)			++	±	±
Lower Urinary Tract Infection	(Minimal in centrifuged specimen)			++	0	0

* Positive in at least one erect specimen.
† Urine culture often positive.

collected on the following day after 30 minutes in an exaggerated lordotic position, standing or kneeling on a chair. The upright lordotic position was found to be impractical for routine use, since because it was uncomfortable it was not properly maintained without constant supervision.

The *Addis test* was performed according to the usual technic.[23]

Determination of albumin was by the turbidimetric method (Exton [85]), using 20 per cent sulfosalicylic acid, three drops added to approximately 5 c.c. of urine in a test tube. Results were read as trace or 1 to 4 plus. In this laboratory, these readings correspond roughly to the following percentages of albumin:

Trace: less than 0.01 gm. per 100 c.c.
1 plus: 0.01–0.05 gm. per 100 c.c.
2 plus: 0.05–0.10 gm. per 100 c.c.
3 plus: 0.10–0.25 gm. per 100 c.c.
4 plus: greater than 0.25 gm. per 100 c.c.

By directive, the total period of hospitalization of these patients was limited to a period of three days. Each case had a thorough history, physical examination, serologic reaction and roentgenogram of the chest, and additional tests, such as blood urea nitrogen, urea clearance and urine cultures, as indicated. Genitourinary consultation was obtained in cases with pyuria or symptoms suggesting urinary tract infection. Time and current directives did not permit routine pyelography or cystoscopy. This was done where manifestly indicated, however, and a representative sample was done in special groups. Some error was probably inherent in mass collections of urines and performance of Addis' counts, taking into consideration the ease with which red cells and casts degenerate. In general, however, results were consistent and appeared reliable. Our criteria for diagnosis are schematically summarized in table 1.

Results

Incidence of Albuminuria

The 600 hospitalized cases constituted approximately 0.5 per cent of the total number examined. Since it was estimated that only about 25 per cent of instances of albuminuria were hospitalized, the approximate total

Table II

600 Cases of Albuminuria (Hospitalized)

Type	Variety	Number	Per Cent
Benign	Transitory	147	24.5
	Orthostatic	154	26
	Lordotic	12	2
	Lordotic-orthostatic	49	8
	Miscellaneous	7	1
	Total Benign	369	61.5
Pathologic	Persistent	138	23
	Glomerulonephritis	42	7
	Pyelonephritis	51	8.5
	Total Pathologic	231	38.5

incidence of albuminuria was calculated as 2 per cent. Table 2 gives the breakdown of types of albuminuria found in the hospitalized group.

In an additional group (211 applicants for West Point), an incidence of 9 per cent (all benign except one) was observed. This difference is probably due to the lower mean age of the group (17 years) and to the prolonged period of stress associated with such competitive examinations.

Types of Albuminuria

1. *Transitory Albuminuria.* This type was present in 147 cases, approximately 24 per cent of the entire group. These transitory cases did

not appear to represent one type of abnormality. It was not possible to subclassify this group accurately. A small number probably represented albuminuria from physiologic stress or fortuitous factors previously described which were not repetitive. A small percentage of this group represented a mild occult form of lordotic albuminuria which could be demonstrated only by the extreme lordotic position, as shown in five of 17 cases with previously negative consecutive urines. Prolonged standing, marching and fatigue may favor the extreme erect lordotic position in predisposed individuals and may reproduce necessary conditions for albuminuria.

Most cases of transitory albuminuria, however, were considered of the emotional variety, based upon some constitutional abnormality of the individual. This was indicated by the frequent history of recurrent albuminuria of many years' duration. Although transitory from day to day, these cases are cyclical or recurrent, presumably when conditions of environmental stress to which the individual is predisposed become operative. Such cases may present albuminuria only under severe emotional tension. The diminishing incidence of albuminuria with increasing age may represent gradual adjustment from the emotional lability of adolescence to the relatively greater equanimity of adult life.

No characteristic clinical picture could be demonstrated in this heterogeneous group. Albuminuria had been a not infrequent cause for previous rejection for military service. Incidence of recent respiratory infection, excess of alcohol, lower genitourinary infection, etc., was not high. Family history was not contributory.

2. *Postural Albuminuria.* The total incidence of albuminuria related to posture was 215, or 36 per cent.

a. Orthostatic: In 154 (or 26 per cent of the entire series), albumin occurred only in the erect position, while in an additional 49, positive urine reactions occurred in both the erect and the horizontal lordotic positions (combined group). Albuminuria was usually mild (from trace to 1 plus), and appeared under various and not necessarily uniform conditions. Most commonly it followed arising from the recumbent position and with activity (63 cases), less frequently immediately upon arising only (47 cases), or on several occasions during the day (32 cases). In 12 cases, proteinuria occurred only following prolonged standing. Albuminuria appeared in the first specimen secreted immediately after arising or activity, i.e., within two hours, and usually promptly disappeared. In 13 of this group, a history of known albuminuria of up to 12 years' duration was elicited.

To determine the influence of the lordotic position upon the orthostatic variety, a small number of these cases was placed in the erect kyphotic position immediately on arising and then, after an interval of bed-rest, in erect lordosis. The assumption was made that if albumin was excreted equally in both erect kyphosis and lordosis, the latter could be excluded as the causative factor. Conversely, a prime influence of the lordotic position would be suggested if albumin appeared in erect lordosis but not in erect kyphosis. In 18

out of 22 individuals, albuminuria was present in erect kyphosis as well as lordosis. It was concluded that in a small percentage of orthostatic albuminuria the erect lordotic position is the activating factor inducing albuminuria. In the majority of cases, however, the orthostatic position per se is a competent cause in inducing albuminuria.

b. Lordotic: The number of cases in which albuminuria followed only the recumbent lordotic position was surprisingly small, i.e., 12. The strain imposed upon renal function by recumbent lordosis apparently is less than that following erect lordosis (Bull [26]). Our previous observations suggest that a small fraction of cases classified as transitory and orthostatic properly belonged in this group. These were borderline cases, as evidenced by their failure to respond to recumbent lordosis as they did to erect lordosis.

c. Combined orthostatic-lordotic: In 49 cases, albuminuria followed both recumbent lordosis and orthostasis. The albuminuria following the erect position in this group was not due to the lordotic posture. Since albuminuria persisted even in the erect kyphotic position, these cases represent positive response to two distinct unrelated postural stimuli, and are both orthostatic (group a) and lordotic (group b) in type.

It appears that in congenital renal defects, various positions, exercise, or a combination of these may cause albuminuria. From a practical point of view, omission of the recumbent lordotic position would have involved missing 12 cases of postural albuminuria. The 49 in the combined group would have been detected in the orthostatic position. The routine inclusion of the practically difficult and unreliable erect lordotic position appeared unwarranted. The effect of the horizontal lordotic posture is fleeting, since in only five did it persist when the posture was maintained. This temporary effect of maintained posture was previously noted in the orthostatic group.

Albuminuria was generally greater in the combined type (from 1 plus to 2 plus). Moderate abnormalities in the Addis count, especially in increased white cell counts or casts, occurred rather frequently in the lordotic and combined group. In six cases of the combined group, albuminuria had been previously recognized for periods up to 19 years. Several cases of this type gave a history suggesting urinary tract infection (acute pyelonephritis), and low back pain and dysuria were frequent complaints. In one instance with moderate albuminuria of the combined type (lordotic and orthostatic), a horse-shoe kidney with hydronephrosis was detected.

In 21 of this combined group, albuminuria was present practically throughout the day, i.e., horizontal lordotic, arising orthostatic, activity and evening, and differed from persistent albuminuria only in the absence of albumin in the urine collected during night recumbency. These cases probably represent somewhat greater degrees of congenital renal lesions.

It appears unreasonable to classify a group of related congenital defects of the kidneys purely upon the particular position most prone to induce albuminuria, especially when, as shown here, several factors may be operating

jointly. As long as such cases of albuminuria are detected and properly classified as postural, further classification into orthostatic, lordotic, or both, is largely academic.

d. Miscellaneous: Seven cases in this series defied classification because of irregular albuminuria, which was nocturnal in several. Four had infections of the lower genitourinary tract; the others were considered to be due to errors, rather than to represent unusual types of albuminuria.

3. *Persistent Albuminuria.* This abnormality was noted in 138 cases, or 23 per cent. In 27 instances, asymptomatic albuminuria had been detected as long as 13 years previously. Seventeen others gave a history of renal disease in childhood, with albuminuria persisting to the present for an average duration of eight years. Combining these figures, 32 per cent of this group gave a history of either nephritis or persistent albuminuria of many years' duration without evidence of significant progression. In 60 per cent of this group there was a significant increase in the excretion of albumin following erect posture or activity, whereas in the remainder, albuminuria was greater in degree and fairly constant. The latter group may represent more severe renal disease, as suggested by the more frequent history of glomerulonephritis or congenital anomalies on urogram. The differential diagnosis from pyelonephritis may be difficult, especially when pyuria is intermittent. Four cases of persistent albuminuria gave a history of previous pyelonephritis. They showed fixed albuminuria, hypertension and low urinary specific gravity, suggesting a moderately advanced renal lesion.

In 19 cases of persistent albuminuria selected at random for intravenous pyelogram, 11 revealed abnormal findings, including four with bifid pelvis, one extensive bilateral staghorn calculus, one calcified post-traumatic kidney, one extensive renal ptosis, one infantile pelvis, one with calyectasis, one with poor bilateral dye excretion, one with pelviectasis and constriction of the ureter.

There were 11 cases with authentic histories of glomerulonephritis in childhood, usually with interval albuminuria, but with no clinical recurrence or other evidence of active renal disease. The interval between the episode of nephritis and current observation extended up to 20 years, with an average of nine years. Red and white cells were currently absent from concentrated urine. Blood pressure and renal function tests were normal. These cases revealed no evidence of active glomerulitis or any progressive renal lesion. The clinical course and current findings suggested a residual static lesion or defect. These cases may represent "healed glomerulonephritis with defect," described by Addis.[22] To recapitulate, approximately 10 per cent of the group with persistent albuminuria gave a history of glomerulonephritis, and about 5 per cent, of pyelonephritis. In 11 out of 19 cases in which routine pyelograms were done, significant abnormalities (usually suggesting congenital defects) were noted.

It is believed that persistent albuminuria represents a moderately advanced stage of renal damage due to various causes, particularly congenital renal anomalies, healed or extremely latent glomerulonephritis and chronic pyelonephritis. The history and findings suggest that in many instances the tempo of the disease process is exceedingly slow. Neither renal impairment nor vascular disease is a conspicuous complication, and this condition apparently may be compatible with normal health for long periods. It is evident that cases of this type justify detailed study, including urography as well as prolonged follow-up. Early detection of cases of pyelonephritis or extensive congenital renal anomalies may insure earlier treatment and prolong life. The long term of this group may also have some bearing on the problem of hypertension. Based upon the recognized latency and relatively benign course of many of these cases, as evidenced by the prolonged duration of persistent albuminuria, without other features of Bright's disease, selected individuals might be utilized for military service in limited capacity.

Chronic Glomerulonephritis

This diagnosis, based upon persistent albuminuria associated with definite microscopic hematuria, usually with casts and epithelial cells, was made in 42 cases (7 per cent). Considering the large number of cases examined and the probability that few could escape detection at pre-induction stations because of the constant albuminuria, the general incidence of this disease does not appear high. Since a number of these cases represent reëxaminations following previous draft rejections, the actual incidence is even lower than indicated. This confirms the general impression that glomerulonephritis is becoming a relatively rare disease.

The initial onset of acute nephritis based upon grossly bloody urine had been recognized in seven instances at periods of from two to seven years (average, four years) prior to this examination. In three other cases, albuminuria had been detected two, five and nine years previously. Twelve cases had recently had mild symptoms, most frequently nocturia, dysuria and dark urine, probably representing recurrent acute glomerulitis.

Nineteen of the group (slightly more than half) gave no history suggesting renal disease and were asymptomatic despite evidence of severe and progressive renal disease. Only eight individuals of the entire group had been under medical observation for renal disease, six following recognized acute glomerulonephritis, merging into the chronic stage, one for albuminuria and another because of unexplained recent hematuria. In most of our cases of chronic glomerulonephritis, the acute stage had been unrecognized, and the chronic stage was detected accidentally in the course of this routine examination.

Hematuria varied from occult amounts (1,000,000 Addis count) to innumerable red cells. In most cases, red cells remained in the range up to 25,000,000 (18 cases), and were over 100,000,000 in only seven. White

cells and epithelial cells were either normal or slightly increased. Casts were variable, being appreciably increased in 23 cases. Albuminuria, although persistent in all specimens, varied considerably. A practically constant rate of excretion was observed in 24 cases, and in 11 it was minimal at night with increase during the day. In general, there was good correlation between the degree of albuminuria and number of casts, but not with the degree of hematuria. Elevation in diastolic blood pressure over 90 mm. Hg was noted in 20, and over 100 in 10. These results represented the mean basal levels obtained after many readings. Hypertension was more frequent in individuals with marked albuminuria and large numbers of casts.

Renal function as measured by maximal concentrating capacity of the urine and other clinical methods was generally within the normal range. In only nine cases was the maximal concentration reduced below 1.020. In five cases with marked constant albuminuria, the urinary specific gravity was fixed from 1.012 to 1.015. Four of these had significant hypertension and marked cylindruria. A correlation existed between the extent and constancy of excretion of albumin and of casts, and the development of hypertension and renal impairment. Nocturnal-diurnal variations in rate of excretion of albumin probably represented less renal impairment than a constant rate of excretion of large amounts of albumin.

Chronic Pyelonephritis

This diagnosis was made in 51 cases, or 8.5 per cent of the series, confirming current estimates concerning the relatively increasing incidence of this disease compared to chronic glomerulonephritis. The diagnosis of this disease is difficult, because pyuria may be intermittent. Some cases in this group were originally considered persistent or orthostatic albuminuria. When rehospitalized months later, pyuria and occasional positive urine cultures were obtained. Intermittence of pyuria may be due to irregular drainage of pus into the urine, or these cases may represent subsequent secondary infection superimposed upon congenital disorders of the kidneys, previously indicated only by albuminuria.

Six cases presented a history of pyelonephritis in childhood. One case gave a history of treatment for prostatitis and several for gonorrhea, but the incidence of infection of the lower genitourinary tract was not large. Three gave a history of albuminuria for several years, but no other finding or treatment. Fifteen (including six cases with a previous history) were irregularly symptomatic, the most common complaints being backache, frequency and dysuria. The three cases with previous albuminuria were asymptomatic and revealed only borderline pyuria (3 to 6 million white blood cells). Including all instances with a prior history, symptoms or albuminuria, there were 18 cases suggesting prior renal disease, and 26 (or over 60 per cent) without any evidence prior to the induction examination to incriminate the urinary tract.

Albuminuria is said to be extremely variable in pyelonephritis, and, as pointed out by Raaschau,[37] a patient may die in uremia from this disease without albuminuria. However, albuminuria is the most important feature in differentiation from infection of the lower genitourinary tract. In this series, by selection, all had shown albuminuria, but eight failed to show albumin at the time of examination; six were orthostatic, and one showed albumin only following horizontal lordosis. Persistent albuminuria was present in the remaining 29 (65 per cent). In 14 cases, the albumin ranged from a trace to plus, in five to 2 plus, and in the remaining 10 it was 3 plus or over. Albuminuria seemed to bear no relation to the degree of pyuria.

Pyuria varied considerably, such variations often occurring at short intervals. Thus a practically normal Addis count might be followed shortly by urines containing many white cells. Addis counts varying from 200,000,000 cells down to 400,000 (normal) were obtained. In 11 cases clinically included in this group on the basis of positive culture or other strong evidence, Addis counts under 4,000,000 were reported. Pus casts were considered of the highest diagnostic significance and were noted in five. Hematuria was rare; values over 400,000 occurred in only 10. Gross transitory hematuria is said to be not unusual and was described in the history in two cases. According to Raaschau,[37] this may occur even in the absence of stone, as a result of hemorrhagic pyelitis or cystitis. Cylindruria of significant degree was noted in 16 cases. This may be the result of the disease, which is largely medullary in distribution, or may represent underlying congenital renal disease.

Renal function as measured by the maximal level of urinary specific gravity and other tests was not significantly reduced. Maximal specific gravities below 1.024 were recorded in 15 cases. Hypertension (diastolic over 100) was observed in 14 cases (approximately 33 per cent). Positive urine cultures were obtained in only eight cases, but these were not performed routinely or frequently, being limited to cases with a referral diagnosis of pyelonephritis. *Staphylococcus albus* and *Escherichia coli* were the usual organisms. Active infections of the lower urinary tract were excluded by urologic examination.

A good deal of study is often required to make the diagnosis of pyelonephritis with assurance. A positive history and albuminuria with manifest pyuria, or positive urine cultures with exclusion of disease of the lower urinary tract, are all useful criteria. Hypertension is rather frequent and is a helpful criterion. The relationship between vascular hypertension and chronic pyelonephritis has been the subject of considerable controversy.[36] The relatively high incidence among young individuals of pyelonephritis, usually in an unrecognized form, indicates the necessity for increased alertness by clinicians for this disease. The group included in this study includes the primary hematogenous variety and perhaps a number associated with congenital renal disease. Statistics on pyelonephritis reveal an increas-

ing incidence with age, especially in males, due to the secondary type associated with urinary obstruction and stasis. Our high incidence in a younger age group is, therefore, the more striking.

Discussion and Summary

A practical, rapid procedure has been developed for the differentiation of various types of albuminuria. It is based upon a collection of consecutive urine specimens over a 24 hour period under set conditions of position and activity. Fluid and dietary restriction renders the 10 hour night recumbent specimen suitable for a urinary concentration test and for the Addis urinary sediment count. In over 600 cases the procedure was found to be practical and to yield accurate, consistent results. Modifications in the method were made from time to time to eliminate cumbersome and routinely unreliable procedures not yielding essential information. The final procedure consisted of the collection of an evening activity specimen, a 10 hour night recumbent, a second two hour recumbent, and the first specimen upon arising. Use of the exaggerated erect lordotic position was found to be impractical under routine ward conditions, and the horizontal lordotic position was found to be relatively uninformative.

The classification of postural albuminuria based on the positions producing albuminuria has no basic clinical validity and at best is of academic interest. The differential diagnosis of various forms of albuminuria (see table 1) requires recognition of common sources of error, particularly in relation to influence of diet, hydration and activity upon excretion and laboratory detection of urinary protein. The importance of urinary dilution, diet and minor deviations from the procedure, particularly as to activity, must be recognized in proper evaluation of this procedure.

In the latter phases of this study, an ambulatory procedure was devised for the purpose of simplification. It was thought that three specimens, including the night recumbent and two after activity, would differentiate adequately between the three major types—benign transient, benign postural and pathologic persistent. It was soon evident that the very simplicity of of the method had inordinately exaggerated minor errors and eliminated many of the checks (multiple specimens and specific gravities) to which we had become accustomed. The ambulatory procedure has since been modified to include two recumbent urines, to exclude the effects of activity during the night. By starting the collection of the night specimen after one hour of bed rest, the effects of activity just before retiring are eliminated. Except in unusually coöperative individuals, however, the standard multiple collection procedure affords the most reliable results.

A variation suitable for rough clinical screening would involve the collection of several recumbent urines, with reliance upon the number of specimens to eliminate the effects of activity or horizontal lordosis. The persistent variety would reveal albumin in all specimens of adequate specific

gravity. Further differentiation of persistent albuminuria would require additional study, including an Addis count and intravenous pyelogram.

Our results confirm the usual estimates indicating the frequency of "benign" albuminuria as compared to other types. The 600 cases in table 2 represent those hospitalized from approximately 2,500 cases detected in approximately 120,000 draft examinees. The hospital group is heavily weighted with postural and persistent pathologic types. Most of the approximately 1,900 cases originally detected but passed for service without hospital study because of subsequent negative urines represent mild, fleeting, transient or postural varieties. Even in the hospitalized group, about 24 per cent failed to show albuminuria in multiple specimens at the time of examination, although three consecutive urines had recently been positive. Including this large transitory component, benign albuminuria accounts for approximately 90 per cent of all cases of this abnormality.

Current concepts of albuminuria have been reviewed. Some popular impressions concerning the physiology and clinical characteristics of this group of abnormalities require reconsideration. Albuminuria is generally classified as benign or pathologic. In the former, excretion of urinary albumin is irregular or intermittent; in the pathologic, it is constant or persistent. Excluding rare fortuitous causes, we have subdivided the benign albuminuria into transitory and postural. The former is apparently the more common variety. An extensive clinical literature has been reviewed, with confirmatory physiologic observations implicating psychogenic factors in constitutionally predisposed individuals as the cause of transitory albuminuria. Such predisposed individuals with labile nervous and vasomotor systems are subject to albuminuria via renal vasoconstriction following conditions of stress. Transitory albuminuria cannot be freely reproduced but is irregularly recurrent or cyclic. Whether such individuals, through repeated renal vasoconstriction, become more subject to renal vascular disease or hypertension is conjectural.

Postural albuminuria represents 36 per cent of the hospitalized group studied. Mild cases may be missed even on serial urine collections, unless a specimen following the erect lordotic position is obtained. Ordinarily, postural cases are readily diagnosed, since albuminuria may be demonstrated at will by various positions causing strain—lordosis, orthostasis or activity. The conditions causing maximal strain vary, and in a considerable percentage, several positions independently induced albuminuria. Despite reports to the contrary,[26] our observations indicate that the erect position, per se, frequently produces albuminuria even when the effect of lordosis is excluded. It is probable that the underlying predisposing cause, precipitable by various postures or activity, is a congenital abnormality of renal structure or circulation. Such defects may be unilateral or bilateral, involving the renal parenchyma, its vascular supply, or even the portal circulation (Bull [28]).

It is important to recognize that both the transitory (vasospastic) and the postural (organic) types are associated with demonstrable impairment of renal circulation and function synchronous with or preceding the phase of albuminuria. The frequency of casts and other formed elements during the period of albuminuria, according to Addis, suggests the existence of an actual though temporary renal lesion. In advanced types of postural albuminuria, urinary albumin excretion becomes almost constant except during recumbency. It is possible that persistent albuminuria may develop in congenital renal disease as the result of secondary pyelonephritis.

No contribution pertaining to the physiology of albuminuria is made as a result of this clinical review. It is interesting, however, to correlate clinical observations with recent physiologic studies in this field. The rôle of renal vasoconstriction in producing albuminuria has been repeatedly verified since the studies by Starr.[19] Renal ischemia, induced by various reflex stimuli such as cold, by adrenalin, ephedrine, hemorrhage or excitement, may induce albuminuria. Albumin is excreted in the stage of dilatation following renal vasoconstriction. Exception is taken to the conclusions of Bull [26] and others that the erect lordotic position is the basic physiologic stress causing postural albuminuria. In the majority of cases of orthostatic albuminuria, the assumption of the erect position even in kyphosis is sufficient to cause albuminuria.

Normally there is a substantial reduction in renal blood flow and function in the erect position and after exercise.[29] Possibly such additional depression of renal tubular function in kidneys already damaged by congenital, inflammatory or degenerative disease may favor urinary loss of albumin. Albuminuria may be unilateral, as originally demonstrated by Rytand [33] and confirmed by Bull.[26] It is too early to determine the rôle of the congenitally short and embedded portal vein (Bull [26]) as an important cause of postural albuminuria. Our own observations and those of others would suggest that congenital renal anomalies play the major rôle in this disorder.

The exact site of the loss of serum albumin into the urine is still controversial. Increased glomerular permeability is granted as the cause of leakage in frank inflammatory or degenerative glomerular disease, although the rôle of tubular reabsorption has recently received increasing recognition. It is difficult to determine in transitory albuminuria, either vasospastic or due to postural hemodynamic effects, whether temporarily increased glomerular permeability or depressed tubular function is responsible. That tubular function may be easily depressed has been shown by the effect of chilled plasma (Dock [32]). In advanced renal disease, both mechanisms can be invoked. With increased glomerular permeability, the excretion of formed elements, particularly red cells, would be anticipated. Actually, this seldom occurs in any type of albuminuria except in glomerulonephritis.

It is our belief that, under certain conditions, albuminuria is in effect an index of renal (tubular) function. With increasing renal (tubular) damage,

albuminuria tends to become more severe and the rate of excretion constant. In milder cases of persistent albuminuria, the rate of excretion is increased by erect posture (additional depression of renal function).

Pathologic albuminurias include that found with chronic glomerulonephritis and chronic pyelonephritis, and a large group of persistent albuminuria without overt clinical cause. This group constituted about 40 per cent of the hospitalized series. Relatively few are missed in routine examination, so that the overall relative incidence of pathologic albuminuria is probably not in excess of 10 per cent. The significance of constant albuminuria, without the changes in the sediment characteristic of known varieties of Bright's disease, is puzzling. In about half of the 138 cases studied, albuminuria had been observed for many years (average eight years) without evidence of progression or deterioration of renal function. This condition does not constitute a single pathologic entity but denotes a stage of renal damage due to latent or very slowly progressing lesions. The latent stage of chronic glomerulonephritis or pyelonephritis and congenital defects may produce constant albuminuria.

Over 10 per cent of persistent albuminurias gave a documented history of glomerulonephritis with subsequent albuminuria but normal sediment and renal function, and absence of vascular complications. These may represent the "healed glomerulonephritis with defect" of Addis, or at least an extremely latent form of the disease. Pyelonephritis without overt pyuria may represent a small percentage of this group. The balance are probably congenital renal lesions. In our series, a high incidence of congenital nephropathy was noted. Other minor miscellaneous causes include trauma, obstructive lesions and calculi. Although not observed in this group, diffuse vascular lesions such as arteriolosclerosis and amyloidosis may produce persistent albuminuria. The necessity for careful study of cases of persistent albuminuria, particularly by urography, is evident.

Chronic glomerulonephritis was the least frequent cause of pathologic albuminuria, with a relative incidence of 7 per cent in the hospitalized group. The disease is evidently becoming rare. More than half of these individuals gave no history of renal disease and, despite the evidence of active nephritis, were totally asymptomatic, being first recognized accidentally by this survey. The controversial problem is again posed whether chronic glomerulonephritis is necessarily the sequel of acute hemorrhagic glomerulonephritis. The youth of the individuals examined in our series renders such negative history relatively more valid than those histories obtained in later life in clinically advanced nephritis. Maintained hypertension above commonly accepted normal levels occurred in 40 per cent.

Chronic pyelonephritis was more frequent than glomerulonephritis, confirming recent observations in the literature. The relative incidence was 9 per cent in the hospitalized group. These cases in younger individuals represent primary (hematogenous) pyelonephritis (sui generis of Raaschau [87]),

compared to the more frequent secondary pyelonephritis associated with obstruction of the urinary tract observed in older age groups. Considering the latter group, the increasing importance of pyelonephritis as a frequent form of Bright's disease is evident. The diagnosis of pyelonephritis is frequently difficult, and may require prolonged observation and all clinical and laboratory facilities available, including urinary cultures and urography. Pyuria may be intermittent. Albuminuria may be variable early and persistent in later stages with more advanced renal injury. The combination of pyuria with either albuminuria or urographic evidence is desirable to localize the infection as renal. Associated hypertension of moderate degree is relatively frequent (33 per cent) and, when present, helps to confirm the diagnosis. Such values in a young age group are significant, and contribute to current discussion concerning the relationship between pyelonephritis and vascular hypertension. Despite the increasing incidence of pyelonephritis (or its recognition), it is probably not sufficiently common to constitute a major cause of vascular hypertension. Conversely, however, hypertension occurs with sufficient frequency in the disease, even with good renal function, to constitute a diagnostic feature and an important complication which may accelerate vascular and renal damage.

Conclusion

1. A standardized procedure for the rapid and reliable diagnosis of various forms of albuminuria is described. It is applicable to the rapid evaluation of large numbers of cases, such as draft examinees, or to routine ward or office study.

2. The results in 600 draft examinees who were hospitalized for study are tabulated and discussed.

3. The high incidence of benign, inconstant albuminuria in young men is reëmphasized. It is estimated that at least 90 per cent of all cases of albuminuria belong in this group.

4. Particular attention is called to one variety of benign albuminuria which is transitory and unpredictable in its occurrence. It is believed that emotional influences are major factors in its production via renal vasoconstriction.

5. Postural albuminuria accounts for the balance of the benign group. The classification of this group is discussed and clarified. It is believed that classification based purely on bodily position has little or no fundamental significance. Lordosis is not the only postural influence causing albuminuria in this group; the erect position and activity also are important influences. Congenital renal anomalies are considered the underlying basis for postural albuminuria. In view of this fact, there is some question as to the unqualified use of the term "benign" for all cases of this condition.

6. Persistent albuminuria without overt evidence of renal disease is the most common variety of pathologic albuminuria. This condition is not a

single pathologic entity but represents a moderately advanced stage of renal damage resulting from a variety of congenital, inflammatory and other causes. Despite the current absence of active glomerulitis, 10 per cent of this group appeared to represent latent or healed glomerulonephritis. Some evidence has been submitted to suggest that many of these cases are due to congenital renal disorders. The necessity for urologic survey and periodic checkup of these individuals is stressed. The clinical history of this group often indicates a slow tempo of progression, especially in those due to latent glomerulonephritis and congenital renal defects. Very few of the series were symptomatic or aware of any renal disease.

7. Chronic glomerulonephritis was the most infrequent variety of renal disease encountered. More than half of the cases discovered were asymptomatic and without knowledge of any prior renal disease.

8. Chronic pyelonephritis was slightly more frequent than glomerulonephritis. The diagnosis is often difficult, since occasionally both albuminuria and pyuria may be intermittent. The disease may be ingrafted upon congenital renal disorders. Hypertension was observed in about one-third of this group.

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THE MECHANISM INVOLVED IN POLYNEURITIS AS EXEMPLIFIED BY POSTDIPHTHERITIC POLYNEURITIS*

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THE toxin of the diphtheria bacillus offers the physician an unusual opportunity to observe the onset and march of signs in polyneuritis. The patient is in the hospital 10 days before the onset of palatal weakness and several weeks before the onset of paralysis of the limbs. Because the etiology of postdiphtheritic polyneuritis is known, a study of 53 such patients may shed light on the mechanism involved in 40 patients with a polyneuritis of unknown etiology but similar to the postdiphtheritic type in its clinical manifestations, spinal fluid and postmortem findings.

Since 1943, diphtheria has increased steadily in Boston, until in 1946 there was an incidence of 157 cases and 10 deaths. In 1949, 223 patients with diphtheria were admitted to the contagious building of the Boston City Hospital, and 11 of these had paralysis. In 1950 there were 60 cases of whom three had neuritis. Owing to the use of antibiotic drugs for sore throat, cultures are omitted, and there has been an increase in the number of patients with postdiphtheritic paralysis. From 1915 to 1943 there were four patients or less per year (a total of 53) in whom the diagnosis of diphtheritic polyneuritis was made.

ANALYSIS OF CASES

The ages of the patients varied from two to 59 years; there were 23 in the first decade, and 31 were males and 22 females.

HISTORY OF INFECTION PRIOR TO THE ONSET OF THE NEURITIS

All but two of the 39 patients with acute faucial diphtheria admitted to the contagious building known as the South Department had positive cultures. In the series admitted directly to the Boston City Hospital, nine patients had been treated for diphtheria by their local doctors, and in five the diagnosis was made by the history of sore throat and the fact that other members of the family had diphtheria. Seven had received no antitoxin.

CRANIAL NERVE INVOLVEMENT

In all 51 of the 53 patients who were examined early enough in the disease to determine this point, the first sign was paralysis of the palate, probably due to neuritis of the tenth cranial nerves. In three to four weeks, 21

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developed paralysis of the ciliary muscle with loss of accommodation. In four to six weeks, weakness of the eye muscles and other cranial nerves followed. Twelve had paralysis of the sixth cranial nerve, 11 of the seventh, eight of the third, five of the ninth, three of the twelfth, two of the fifth and one of the eleventh cranial nerve.

Muscular System

Both the distal and proximal muscle groups were involved in the extremities, but in many the weakness did not progress to complete paralysis. Trunk muscles were also weak in the majority of the patients, and many had difficulties with respiration due to both diaphragmatic and intercostal weakness.

Sensory System

It is probable that all patients suffered sensory disturbances about the time that the deep reflexes were lost. All the adult patients, the only ones able to describe sensory changes, complained of numbness and tingling of the extremities, on sensory examination they were found to have loss of light touch and pain sensation. Some of the patients developed an ataxic gait, evidence of diminished position and vibration sense.

Deep Reflexes

In 10 cases in which records of careful and frequent physical examinations were made early in the disease, it was found that the *loss of deep reflexes preceded the weakness of the muscles by from four to 12 days (average, 7.9 days)*. There were six patients, not included in this series, who had palatal paralysis followed in several weeks' time by disappearance of deep reflexes without evidence of weakness of the extremities. Five of these patients were young children, so there might have been sensory loss had it been possible to detect it. The deep reflexes were absent in all but two patients, and in those they were extremely sluggish.

Respiratory Failure

Five of these patients died from respiratory failure. Four were in the first decade and one in the third. One seven year old patient had been placed in the respirator, but four of the patients were admitted in the days before the existence of a respirator.

Myocardium

Fifteen of the 34 patients admitted early in the disease to the contagious wards had evidence of myocardial damage. This was demonstrated by electrocardiographic changes, which varied from slowing of conduction time to complete auricular ventricular block. It is probable that the diphtheria toxin affects both the conduction tissue and the muscle fibers of the heart.[1]

Spinal Fluid

The cerebrospinal fluid was examined in four of the patients in this series, and in two recent patients, one from the Boston City Hospital and one from the Massachusetts General Hospital. The spinal fluid was clear and colorless. Initial pressures were normal. The total protein varied from 198 to 51 mg. per 100 c.c., the cell count from 0 to 4, one gold sol had a slight midzone and one an end zone rise, and the Wassermann reactions were negative. The typical Guillain-Barré syndrome of disassociation of cells and protein was present.

Treatment

If sufficient amounts of antitoxin were given on the first day of the diphtheria, it is probable that very few patients would develop diphtheritic polyneuritis.[1] The increasing tendency of physicians to administer antibiotics without bacteriologic diagnosis undoubtedly contributes to the delay in giving proper therapy to many patients.

Final Results

Five of the 53 patients died and 48 recovered completely. The average time of recovery was three months, and the reflexes returned last. In the five fatal cases, antitoxin had been started late or not at all, and the patients had been admitted after the onset of paralysis.

Chemistry of the Diphtheria Toxin

Diphtheria toxin is a protein containing five amino acids,[2] and it is completely precipitated by another protein, diphtheria antitoxin.[3] Proof that the toxin does not act directly on the nerves is afforded by the length of time before the onset of even palatal paralysis in diphtheria.

Animal Experiments

Toxin alone injected either intramuscularly or intravenously caused paralysis, and toxin mixed with nerve tissue lost none of its toxicity. Intraneural injections of toxin produced a mild paresis similar to that produced by saline solution, which did not resemble a true diphtheritic paralysis.[4]

Polyneuritis Due to Cutaneous Diphtheria

Among neither British nor American troops was there a relationship between the cutaneous sore and the location of the paralysis.[5, 6]

Similarities Between Polyneuritis of Unknown Etiology and Postdiphtheritic Polyneuritis

In the so-called infective polyneuritis with facial diplegia, as great a variety of cranial nerve palsies may occur as with the type due to diphtheria

toxin.[7] Of 26 patients described by Forster et al. at the Boston City Hospital, 22 had paralysis of the seventh cranial nerve, 15 of the ninth and tenth, six of the eleventh, five of the fifth, three of the twelfth and one each of the third and sixth cranial nerves. In 50 per cent there was a history of infectious disease about three weeks prior to the onset of muscle weakness. The mortality was 42.3 per cent, despite the use of the respirator.

There are minor differences: Instead of the tenth cranial nerve, the seventh is almost universally affected. The extraocular muscles are usually spared, whereas about one-quarter of the patients with postdiphtheritic paralysis complained of diplopia. Although almost half of the postdiphtheritic group had ciliary paralysis, this is unknown in polyneuritis with facial diplegia. In postdiphtheritic polyneuritis there is more sensory involvement, and the weakness is not always generalized or severe.

The spinal fluid in both shows the albumin-cytologic dissociation, but this dissociation is not by any means complete. Of 26 patients of Forster et al., seven had normal spinal fluid protein and 12 had a cell count above five. In both diseases the nerve roots and cranial nerves show destruction of myelin, a few lymphocytes, little change in the axis cylinders and axonal changes in anterior horn cells. A summary of 50 fatal cases of the Landry-Guillain-Barré syndrome received by the Army Institute of Pathology agrees with these findings.[8]

In addition to the 26 patients just described, I should like to mention 14 others with a similar clinical picture. In the past 15 years at the Massachusetts General Hospital there have been 11 patients with diabetes, four of whom have had paralysis of the legs and seven of all four extremities. Three have had facial diplegia, and all had a high spinal fluid protein without an increase in cell count. The protein has ranged from 399 to 80 mg. One of the 26 patients of Forster et al. had diabetes. I have also seen a patient with dermatomyositis and polyneuritis, who had increased protein and normal cell count in the spinal fluid.

During the study of the incidence of all types of polyneuritis over a period of 26 years at the Boston City Hospital,* two patients were encountered who had had the syndrome following injection of animal proteins. One had had tetanus antitoxin, and one had received her thirteenth in a course of 16 vaccinations against rabies. Both had paralysis of all four extremities, facial diplegia and increased protein in the spinal fluid. Here there can be no doubt of an allergic response of the nerve cell to a foreign protein.

Though unaccompanied by cranial nerve involvement or increased spinal fluid protein, the polyneuritis due to conditioned deficiency states and chemical poisoning may also be due to interference with enzymatic system of the nerve cell. In the study just mentioned, 1,225 Boston City Hospital records bearing the diagnosis "peripheral neuritis" were abstracted, and

* Assistance in the preparation of this material was furnished by the personnel of the Works Progress Administration, Official Project, No. 17579.

827 patients were thought to have polyneuritis. Of the group having conditioned deficiency states, 568 had alcoholic neuritis and 26 had polyneuritis following prolonged vomiting or diarrhea. Of the 69 patients who had paralysis following chemical toxins, 47 had ingested tricresol phosphate in Jamaica ginger; the paralysis of 13 was due to lead, of seven to arsenic, of one to sulfanilyl sulfanilamide and of one to sulfamethylthiazole.

Summary

Postdiphtheritic polyneuritis in 53 patients has been remarkably consistent in its course. There is a weakness of the palate about 10 days following the acute infection. About four to five weeks later the patient experiences numbness and tingling of the arms and legs, and the deep reflexes cannot be obtained. Seven to eight days after these symptoms, peripheral sensory loss and weakness of the extremities and even of the trunk muscles follow. At the same time, other cranial nerve palsies develop in about two-thirds of these patients. The nerves to the eye muscles are particularly susceptible to the diphtheria toxin.

The spinal fluid exhibits the Guillain-Barré syndrome of an increase in protein without an increase in cell count more consistently than does the disease described by Guillain and Barré themselves.

The mortality rate was 9.4 per cent. All the fatalities occurred in patients who had received antitoxin either late in the disease or not at all. Paralysis was also seen when the correct diagnosis had been delayed or missed. In this series, postdiphtheritic polyneuritis was not decreasing in frequency, and in recent years the indiscriminate use of antibiotics is increasing the number of delayed diagnoses.

Conclusions

The clinical and spinal fluid findings of 53 patients with postdiphtheritic paralysis have been compared to those of 40 patients with polyneuritis of unknown etiology. Of these 40 patients, 13 had had an infectious disease, 12 had diabetes, one had dermatomyositis, and two had received injections of animal proteins. It is likely that an allergic response of the nerve cell to a foreign substance is involved in both the polyneuritis due to diphtheria toxin and that of unknown etiology. In that case, if used early in the course of the disease, ACTH or cortisone should be effective in both.

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THE EFFECTS OF INTRAVENOUSLY ADMINISTERED VERATRUM VIRIDE IN HYPERTENSIVE AND NORMOTENSIVE SUBJECTS *

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Introduction

Recent studies by Freis and his co-workers have demonstrated that veratrum viride produces a fall in blood pressure not associated with a change in cardiac output or a significant diminution in blood flow to vital organs. The effects are generally vasodilator and may be mediated through the central nervous system.

Freis [2] and Hite [3] have shown that the blood pressure can be significantly lowered in most hypertensive patients when veratrum viride is given orally in sufficient amount; however, effective dosage varies widely and must be determined by individual trial in each patient. Since the preparations employed were extracts of mixtures of veratrum alkaloids, variable potency of the drug and the variable nature of hypertension have been implicated as reasons for the difficulty in predicting the degree of depressor effect. Nevertheless, studies with a refined alkaloid mixture administered orally [4] and with protoveratrine administered intravenously [5] have not eliminated this problem in dosage determination.

The present study was undertaken to determine whether correlations between individual responsiveness to veratrum viride given intravenously in a fixed dose, and the type and severity of the disease, could be elucidated. In addition, the effects of repeated doses and dose acceleration of veratrum viride and the effects of atropinization were also investigated.

Materials and Methods

Veratrone,† a non-alcoholic extract of the alkaloids of veratrum viride containing 2.5 mg. per c.c., was employed in the study. To insure a constant potency of the preparation in the experiment, a single batch of the drug was obtained from the manufacturer and this was used throughout. *All injections were given intravenously.*

Blood pressures were determined with a standard arm cuff and mercury manometer, and all readings were made by one observer. With the patient

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† Veratrone was supplied by Parke, Davis & Company through the courtesy of Dr. E. C. Vonderheide.

at rest in the supine position, blood pressures were taken at intervals of one minute until three to five consecutive readings were consistent. The initial blood pressure (IBP) represents an average of these readings. Following injection, pulse rate and blood pressure were recorded at one minute intervals for 20 minutes, and as often as necessary thereafter until the blood pressure had returned to its previous levels or had stabilized. The "Veratrone floor" represents the lowest blood pressure reached following injection of the drug, and this usually was achieved during the first 20 minutes after injection. The response of the pulse rate was considered in terms of the rate per minute at the time of maximal blood pressure effect, e.g., at the "Veratrone floor."

The clinical data accumulated for the group of hypertensive patients studied included sex and surface area, the latter calculated from the height and weight according to the DuBois body surface chart.[6] Funduscopic examination was done in all patients and they were graded from I to IV, according to the Keith-Wagener[7] classification. An estimation of renal function was made from the level of the blood urea nitrogen and the rate of phenolsulfonphthalein excretion following intravenous administration of the dye. Whether or not the patient was digitalized was also recorded. The diagnosis of preëxisting renal disease was made on the basis of history and course of the disease.

The experiment was divided into four phases:

(1) Ten hypertensive patients were studied in paired experiments to compare the effects of Veratrone given alone, and Veratrone given simultaneously with atropine sulfate.*

(2) Thirty-eight hypertensive patients were give a single dose of 0.2 c.c. of Veratrone. This group included 26 with the clinical diagnosis of benign essential hypertension of varying severity, eight with malignant hypertension, and four with chronic pyelonephritis and hypertension. Grade IV retinopathy constituted the criterion for the diagnosis of malignant hypertension, and among the eight were five in whom the malignant phase was superimposed on chronic renal disease.

(3) Ten normotensive subjects were tested with 0.2 c.c. doses of Veratrone in a manner similar to those with hypertension.

(4) a. In order to determine whether the depressor response to Veratrone was altered by repeated administration, five of the hypertensive patients were given 0.2 c.c. doses at repeated intervals.

b. The depressor response to gradually increasing dosage (dose acceleration) of Veratrone was studied in seven of the hypertensive patients. Starting with 0.06 c.c., the dose was increased until toxic symptoms prevented further testing. Five of the seven were then given repeated 0.2 c.c. doses in a further study of the effect of repeated interval administration.

*As will be pointed out later in this paper, atropine sulfate produced no significant change in the blood pressure fall due to Veratrone. It was therefore used routinely in all subsequent phases of the experiment. The dosage employed varied from 0.8 mg. to 1.2 mg. and was mixed with Veratrone prior to the injection.

This group of 12 patients included three with malignant hypertension and nine with essential hypertension of varying degrees of severity. One of the patients with essential hypertension was studied at a time when his blood pressure was within normal limits.

Results

The depressor responses to Veratrone have been calculated as percentile fall in systolic blood pressure, diastolic blood pressure and mean blood pressure (average of systolic and diastolic), as determined from the IBP and the "Veratrone floor." Since the correlations to be presented show no statistical difference for the three values, the results will be presented only in terms of the mean blood pressure (MBP).

(1) *Effect of Atropine on the Veratrone Response* (*table 1*)

(A) Blood Pressure Response

In the 10 patients who were given Veratrone alone and Veratrone plus atropine in the paired studies, only one (W. S.) showed any appreciable decrease in percentile fall in MBP when given atropine. There was no significant difference between the mean depressor responses of each group ($p < 0.5 > 0.1$).

Although the "floors" were essentially the same, the fall in blood pressure when atropine was given was not as precipitous, as is illustrated in two patients in figure 1.

(B) Pulse Rate Response

Veratrone alone caused a fall in pulse rate in nine of the 10 patients. When atropine was administered, the pulse rate increased during the de-

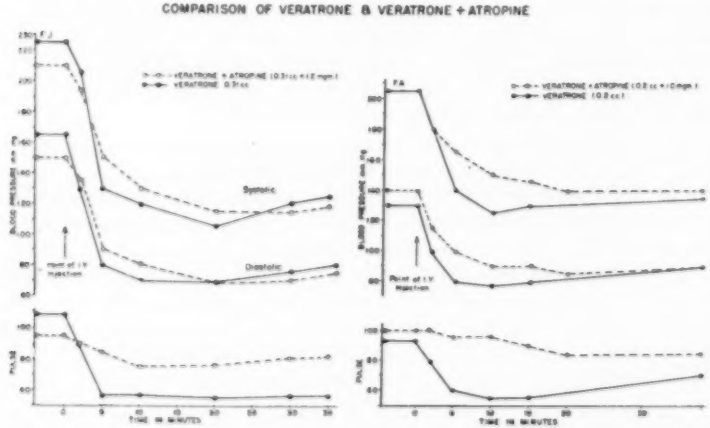

Fig. 1. Comparison of the effects on blood pressure and pulse rate of intravenous administration of Veratrone alone, and of Veratrone plus atropine sulfate.

TABLE I

Comparison of Effects of:

Case	Veratrone Alone							Veratrone plus Atropine Sulfate								
	Veratrone Dose (c.c.)	Effect on Blood Pressure				Effect on Pulse		Nausea and/or Vomiting	Veratrone Dose (c.c.)	Atropine Dose (mg.)	Effect on Blood Pressure				Effect on Pulse		Nausea and/or Vomiting
		Initial Blood Pressure	Veratrone Floor	Per cent Fall in Mean Blood Pressure (MBP)	Time of Maximal Fall (Minutes)	Control Rate/Minute	At Veratrone Floor Rate/Minute				Initial Blood Pressure	Veratrone Floor	Per cent Fall in Mean Blood Pressure (MBP)	Time of Maximal Fall (Minutes)	Control Rate/Minute	At Veratrone Floor Rate/Minute	
		(mm./Hg)									(mm./Hg)						
Fa. J.	.33	227/162	104/68	56.0	18	108	54	N	.33	1.2	208/150	112/70	49.2	27	95	78	0
F. A.	.20	205/128	124/78	39.3	10	92	52	0	.20	1.0	205/140	136/88	35.0	20	100	80	0
J. Po.	.20	175/111	120/88	27.3	8	75	64	0	.20	0.8	150/110	120/86	20.8	12	78	84	0
R. H.	.20	165/108	100/60	41.3	14	86	95	N&V	.20	1.2	171/106	120/80	27.8	25	80	106	N&V
M. H.	.20	197/112	130/78	32.7	8	65	40	0	.20	1.2	200/117	125/90	32.1	10	60	120	0
J. H.	.20	173/119	130/75	29.9	13	84	72	0	.20	1.2	177/112	125/70	32.5	21	84	72	0
F. I.	.20	191/127	170/115	10.2	7	86	76	0	.20	1.0	188/138	155/116	17.2	10	92	90	0
W. S.	.20	195/128	104/70	46.0	14	72	52	N&V	.20	1.2	175/125	145/100	18.4	12	78	126	N&V
D. Z.	.20	161/123	142/108	12.0	9	88	68	0	.20	1.2	165/123	120/90	27.1	15	88	124	N&V
L. M.	.20	156/114	90/68	40.0	8	76	68	0	.20	0.8	150/90	110/68	25.8	9	68	76	0
			Mean: 34.0									Mean: 28.5					
			S.D.: ±16.5									S.D.: ± 8.85					
			S.E.: ± 5.2									S.E.: ± 2.80					

Significance of Difference of Means: $p < 0.50 > 0.10$

pressor response in six patients, and fell only slightly in the remaining four. In one patient (M. H.), the pulse rate actually doubled at the time of maximal depressor response.

(C) Side Reactions

Although atropine prevented the marked sweating which accompanies the intravenous administration of Veratrone, it did not alter the side reactions of vomiting and nausea. Two patients who developed nausea and vomiting with Veratrone alone had these symptoms as severely with Veratrone and atropine. One patient with marked nausea with Veratrone did not experience any when atropine was administered; another who had no symptoms with Veratrone alone developed nausea and vomiting when atropine was given simultaneously.

(2) *Relation of Clinical State of the Hypertension to the Veratrone Response*

Table 2 presents the clinical data, the effects on blood pressure and pulse rate, and the incidence of nausea and/or vomiting in each of the 38 hypertensive patients who were given a single 0.2 c.c. dose of Veratrone.

(A) Depressor Response

The mean percentile fall in MBP for the 38 hypertensive patients was 27.0 per cent; the median of the group fell between 25.9 per cent and 26.0 per cent.

The percentile fall in MBP was subjected to Chi square analysis against each of the variables listed under clinical data in table 2 and against the initial diastolic blood pressure, initial systolic blood pressure and the occurrence of nausea and/or vomiting. With the continuous variables, e.g., the percentile fall in MBP, the initial blood pressures and the surface area, median values were used to separate the cases into two groups. The level of blood urea nitrogen, the phenolsulfonphthalein excretion and the degree of retinopathy were considered as noncontinuous variables, and cases were divided into two groups, on the basis of whether blood urea nitrogen was greater or less than 25 mg. per cent, phenolsulfonphthalein excretion was greater or less than 30 per cent in one-half hour or 45 per cent in one hour, and fundi were Grade I and II, or III and IV, respectively. As concerns the clinical diagnosis, separation was made into a group consisting of those with malignant hypertension, and a group including all others.

Chi square and p values for each of these variables are presented in table 3. The only significant correlation of the percentile fall in MBP is to the level of the initial diastolic blood pressure ($p < 0.05 > 0.01$). The correlation is a negative one, in that patients with higher initial diastolic blood pressures showed a lesser percentile fall to Veratrone.

(B) Time of Maximal Depressor Response

The data indicate that the majority of the patients showed their maximal fall in blood pressure within 15 minutes of the intravenous injection. The mean for the group was 11.4 minutes.

TABLE II

Case	Clinical Data							Effect on Blood Pressure				Effect on Pulse Rate		
	Sex	Clinical Diagnosis*	Body Surface (Meters²)	BUN (mg. %)	PSP Excretion	Fundi	Digitalis	Initial Blood Pressure	Veratrone Floor	Per cent Fall in Mean Blood Pressure (MBP)	Time of Maximal Fall (Minutes)	Control Rate/ Minute	At Veratrone Floor Rate/ Minute	Nausea and/or Vomiting
								(mm./Hg)						
N. W.	F	BEH	1.73	10	40% in ½ hr.	I–II	0	196/131	170/125	9.8	6	76	100	N
I. O'L.	F	CPN→MH	1.52	—	15% in ½ hr.	III–IV	+	213/122	190/110	10.4	17	80	108	N&V
D. H.	F	MH	2.08	5	70% in 1 hr.	IV	0	172/121	150/110	10.6	8	86	112	0
J. B.	M	CPN	1.76	16	45% in ½ hr.	I	0	193/124	166/112	12.1	5	72	82	0
D. T.	M	BEH	1.91	15	—	III	+	211/121	190/100	12.6	7	76	76	0
F. I.	M	MH	1.71	25	10% in ½ hr.	IV	+	188/137	155/114	17.2	10	100	96	0
A. S.	F	BEH	1.86	6	40% in ½ hr.	II	0	197/155	170/120	17.8	6	72	92	0
W. S.	F	BEH	1.63	6.5	80% in 1 hr.	II	0	175/125	145/100	18.4	12	78	126	N&V
S. C.	F	CPN→MH	1.33	200	5% in ½ hr.	IV	0	197/122	155/105	18.5	12	84	96	0
J. Po.	F	BEH	1.83	10	—	II	0	150/110	120/86	20.8	12	78	84	0
M. N.	F	BEH	1.71	10	45% in 1 hr.	II	0	200/135	150/115	20.9	5	74	92	0
Fa. J.	F	BEH	1.72	12	90% in 1 hr.	I	0	166/125	130/100	21.0	5	78	100	N
E. D.	M	BEH	1.58	65	15% in 2 hr.	III	+	206/133	159/108	21.0	15	95	90	0
P. S.	F	BEH	1.80	7.5	80% in 1 hr.	II	+	196/128	148/108	21.0	6	80	96	0
R. H.	M	BEH	1.56	20	—	II	0	151/105	114/85	22.0	11	92	100	N
M. O.	F	BEH	1.57	7	30% in ½ hr.	II	0	220/118	166/96	22.5	13	84	88	N
R. B.	F	CPN	1.51	9.5	30% in ½ hr.	II	0	186/129	140/100	23.8	20	72	138	N&V
F. N.	F	CPN→MH	1.50	25	20% in 1 hr.	IV	0	197/141	145/110	24.0	10	96	92	0
L. M.	M	BEH	1.77	10	—	I	0	150/90	110/68	25.9	9	68	76	0
H. L.	M	BEH	1.98	17	38% in ½ hr.	II	0	172/117	126/98	26.0	7	76	92	0

TABLE II (*Continued*)

Case	Clinical Data							Effect on Blood Pressure				Effect on Pulse Rate		
	Sex	Clinical Diagnosis *	Body Surface (Meters²)	BUN (mg. %)	PSP Excretion	Fundi	Digitalis	Initial Blood Pressure	Veratrone Floor	Per cent Fall in Mean Blood Pressure (MBP)	Time of Maximal Fall (Minutes)	Control Rate/ Minute	At Veratrone Floor Rate/ Minute	Nausea and/or Vomiting
								(mm./Hg)						
J. Pa.	M	CGN→MH	1.75	45	17% in 1 hr.	IV	0	149/110	110/80	26.7	6	80	88	0
D. Z.	F	BEH	1.36	10	—	II	0	165/123	120/90	27.1	12	88	124	N&V
R. H.	F	BEH	1.73	16	40% in ½ hr.	I–II	0	171/106	120/80	27.7	25	80	106	N&V
S. S.	F	BEH	1.67	10	—	II	0	168/112	120/80	28.6	10	76	84	0
E. E.	M	BEH	1.87	17.3	35% in ½ hr.	III	0	195/128	130/95	30.4	8	84	92	0
Fr. J.	M	MH	2.04	15	28% in 1 hr.	IV	+	180/125	130/80	31.1	11	88	84	0
C. L.	M	BEH	1.90	11	—	II	0	172/110	110/80	32.5	10	80	80	0
J. H.	M	BEH	2.05	13	30% in ½ hr.	I	+	177/112	125/70	32.6	21	84	72	0
M. H.	F	BEH	1.68	15	30% in ½ hr.	II	+	200/117	125/90	32.7	10	60	120	N&V
L. Br.	F	BEH	1.63	15	70% in 1 hr.	I–II	0	190/119	118/86	34.0	15	72	100	N
V. G.	F	BEH	1.44	12	45% in 1 hr.	I–II	+	171/110	115/70	34.0	18	80	80	0
F. A.	F	BEH	1.66	16	65% in 1 hr.	II	+	205/140	136/88	35.0	20	100	80	0
P. St.	M	CGN→MH	2.02	24	10% in ½ hr.	IV	0	193/130	120/90	35.0	5	86	92	0
L. Ba.	F	BEH	1.96	9.5	—	II	0	194/103	120/70	36.0	15	72	80	N
E. B.	F	CPN	1.58	50	—	III	+	225/110	135/70	38.6	12	72	68	0
S. W.	F	CPN	1.47	16	30% in 1 hr.	II	+	150/100	86/62	40.8	15	104	96	0
J. H.	M	BEH	1.63	17	—	II	0	214/124	78/60	59.1	21	100	110	0
A. H.	F	BEH	1.42	15	—	I	0	241/114	90/50	60.5	11	68	92	N
			Median: 1.715					Median: 191.5/121.5		Median: 25.95				
										Mean: 27.0	Mean: 11.4			
										SD = ±11.3	± 5.37			
										SE = ± 1.84	± 0.87			

* BEH: Benign Essential Hypertension. MH: Malignant Hypertension. CPN: Chronic Pyelonephritis. CGN: Chronic Glomerulonephritis.

TABLE III

Per Cent Fall in MBP Correlated to:	Chi Square	p*
Sex	.454	0.5
Clinical Diagnosis	.631	0.4
Surface Area	.111	0.7
Blood Urea Nitrogen (37 cases)	.930	0.3
PSP Excretion (27 cases)	.084	0.7
Fundi	.489	0.5
Digitalization	.414	0.5
Initial Systolic BP	.951	0.3
Initial Diastolic BP	5.15	<0.05>0.01
Nausea and/or Vomiting	.114	0.7

* Probability that the observed change could have been due to chance a one. Values of p of 0.05 or less are usually considered significant.

The duration of the blood pressure fall varied considerably. Usually, by the end of 20 minutes it had begun to rise, and by the end of one hour had returned to pretest levels. However, in a few patients it remained below control levels for two to three hours.

(C) Response of Pulse Rate

Fall in pulse rate was minimized by the use of atropine sulfate; in fact, 27 patients showed a rise, while the remaining 11 showed no change or fall. If the 38 patients are divided according to whether or not they were digitalized, it is apparent that most of those whose pulse rate did not rise were in the digitalized group. Of the 12 digitalized patients, nine showed no change or a fall, while only three had an increase in pulse rate; on the other hand, of the 26 undigitalized patients, only two showed no change or a fall, while 24 developed a rise in pulse rate. Chi square analysis revealed a high degree of significances ($p < 0.01$), indicating that digitalis enhances the pulse-slowing effect of Veratrone.

TABLE IV

Response of Normals to Veratrone

Case	Effect on Blood Pressure				Effect on Pulse Rate		Nausea and/or Vomiting
	Initial Blood Pressure	Veratrone Floor	Per cent Fall in Mean Blood Pressure	Time of Maximal Fall (Minutes)	Control Rate/Minute	At Veratrone Rate/Minute	
	(mm./Hg)						
H. Ba.	114/71	110/70	2.7	9	80	84	0
J. C.	116/70	104/74	4.3	12	70	116	N
A. S.	109/72	100/70	6.1	19	80	92	0
W. C.	101/68	90/64	8.9	9	70	100	0
H. Be.	111/66	98/60	10.7	6	72	114	0
L. W.	102/68	90/60	10.9	7	60	80	0
J. I.	137/73	105/56	23.4	3	104	120	0
J. M.	112/79	66/48	40.4	10	104	100	0
W. G.	115/70	70/40	40.5	6	92	88	0
S. N.	112/88	55/40	52.4	6	82	92	N

Mean: 20.5
SD: ±18.5
SE: ± 5.85

(3) *Effect of Veratrone in Normotensive Subjects* (*table 4*)

The mean percentile fall in the 10 normotensive subjects was 20.5 per cent. This was not significantly different from that in the hypertensive group ($p > 0.10$).

Time of maximal fall was essentially similar to that seen in the hypertensive group, and all but two showed a rise in pulse rate.

(4) *Effect of Repeated Doses of Veratrone and of Dose Acceleration*

(A) Figure 2 illustrates the effect of repeated doses of 0.2 c.c. of Veratrone in five patients. The time intervals between doses varied from as long as two weeks (patient L. B.) to as frequently as 13 doses in 16 days (patient F. N.). No constant evidence of the development of tolerance was apparent.

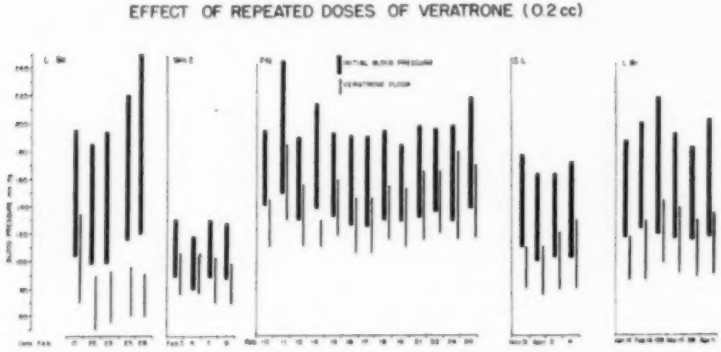

FIG. 2. Blood pressure responses in five patients who received repeated 0.2 c.c. doses of Veratrone.

(B) Figure 3 illustrates the effect of doses of increasing size (dose acceleration), from 0.06 c.c. to as high as 0.45 c.c., in seven patients, five of whom were then subjected to repeated 0.2 c.c. doses. Again, the time intervals between doses varied. The limiting factor in the size of the dose in each instance was the appearance of nausea and/or vomiting. The data indicate that the magnitude of the depressor response did not increase proportionately to the dose increase, but tended to "level off." When repeated 0.2 c.c. doses were then given in five of the patients, there was again no evidence of the development of tolerance, except in patient J. Pa.

(5) *Postural Hypotension*

Blood pressure was recorded in 18 patients when they were asked to sit up at the completion of the test, and in eight of them a depressor response was noted. Figure 4 illustrates this effect in one of the eight responders. A fall in systolic blood pressure occurred, while the diastolic pressure remained relatively constant and the pulse rate rose markedly. This postural change gradually disappeared as the effect of Veratrone faded, and the blood

pressure in the recumbent position returned to normal levels. Postural changes prior to Veratrone administration in these patients were not studied.

(6) Side Effects and Toxicity

All patients experienced a similar subjective sensation following the intravenous injection. This consisted of a feeling of warmth, which usually started in the anterior chest within two to three minutes of injection, and gradually spread over the body, reaching its maximum before or at the time

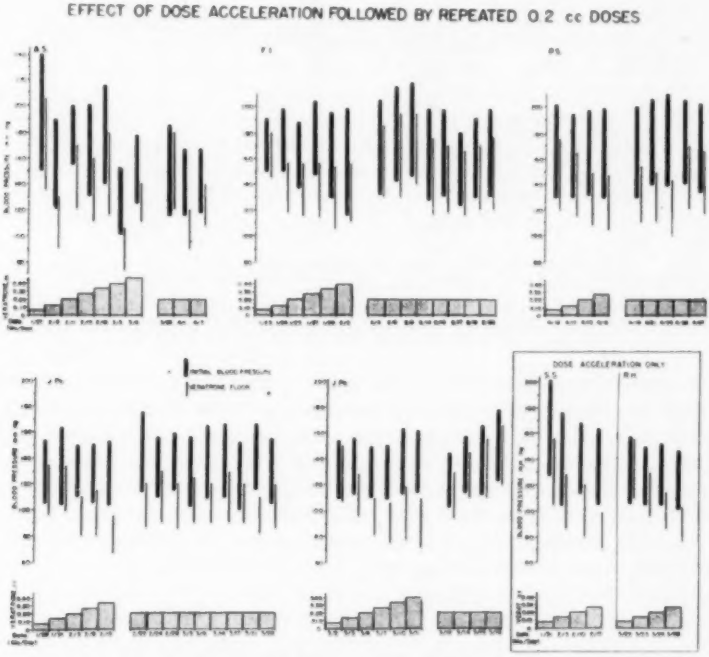

FIG. 3. Blood pressure responses in seven patients who received gradually increasing doses of Veratrone, and were then subjected to repeated injections of 0.2 c.c. The inset in the lower right-hand corner of the chart shows the responses in two patients who received only the gradually increasing doses.

of maximal response in blood pressure. It was variously described as a substernal or epigastric burning or as a "choking in the throat."

Thirteen of the 38 patients with hypertension and two of the 10 normotensive subjects experienced nausea and/or vomiting with the 0.2 c.c. dose (tables 2 and 4). However, in the dose acceleration studies, nausea and/or vomiting appeared eventually in all patients, and were the limiting factors to further increase in the size of the dose. Although nausea and vomiting

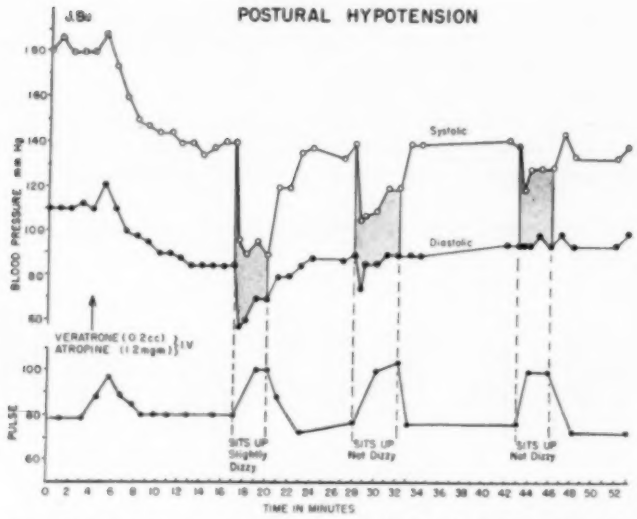

FIG. 4. The effect on blood pressure and pulse rate of rising from the supine to the sitting position following administration of 0.2 c.c. of Veratrone.

thus appeared to be inevitable concomitants of the drug action, the threshold in their development varied among individual patients. Furthermore, when a fixed dose was given, their occurrence was unrelated to the degree of the depressor response (table 3). It was our impression that patients who vomited or had severe nausea with the 0.2 c.c. dose were often individuals with hysterical personalities, who showed considerable emotional reaction to the test. In their clinical histories, nausea and vomiting were frequent symptoms in reaction to various stresses.

DISCUSSION

It was again demonstrated that prevention of bradycardia by atropine did not significantly influence the vasodepressor effect of veratrum viride.[1] In addition, blood pressure falls were not significantly diminished despite the production in some cases of marked tachycardia following atropinization, further establishing that bradycardia is not essential to this action. However, it would appear that the use of atropine did make the fall in blood pressure less precipitous, especially in cases which showed a marked bradycardia when given veratrum alone. Freis [1] has pointed out that the initial drop in blood pressure following veratrum viride may be associated with a slight fall in cardiac output; bradycardia may be responsible for this effect.

The data on pulse rate indicate a relationship between digitalis and the bradycardia produced by veratrum viride. The chemical similarity between

the veratrum alkaloids and digitalis glycosides has been mentioned by Krayer and Acheson,[6] and the potentiation of digitalis effects on rate and rhythm in the electrocardiogram by protoveratrine has been studied by Meilman and Krayer.[5] Our data indicate that in digitalized patients, atropine was not so effective in preventing bradycardia due to veratrum viride as it was in nondigitalized patients. The combination of digitalis and veratrum viride apparently increases vagal tone to an extent which cannot be overcome by atropine sulfate in the doses given, as it was in the nondigitalized patients, most of whom actually developed tachycardia. However, as will be discussed later, digitalis had no effect on the depressor action of veratrum viride.

The results showed a wide range in the percentile fall in MBP in the hypertensive group. A similar range was noted in the normotensive subjects, and the mean percentile fall in both groups was not significantly different. Moreover, in the hypertensive patients, the percentile fall in MBP showed no correlation with a variety of clinical factors. These included the surface area and the sex of the patient, whether or not he was digitalized, and the state of the hypertensive disease as reflected in renal function, funduscopic changes, and the level of the initial systolic blood pressure. However, a significant correlation between the initial diastolic blood pressure and the percentile fall in MBP was noted. Patients whose initial diastolic blood pressures were greater than the median for the entire group showed a lesser percentile fall in MBP.

The diastolic blood pressure is usually considered the best measure of the degree of peripheral resistance, although of itself it does not indicate the clinical severity of the disease or the extent of fixed and irreversible arteriolar damage. The effector site for the depressor action of veratrum has not been established; however, it is perhaps possible that the degree of peripheral resistance may become too great to be overcome by veratrum action, regardless of whether this is a positive effect through active vasodilatation or a negative one through inhibition of vasoconstrictor influences.

The similarity of the depressor effects in the hypertensive and the normotensive groups suggests that veratrum may act not on mechanisms responsible for hypertension per se, but directly on physiologic mechanisms which normally maintain blood pressure. It is of interest in this regard that Meilman and Krayer, commenting on the probable existence of a receptor for the veratrum effect in the left ventricle, suggest that this is the same receptor which results in the fall in blood pressure associated with myocardial infarction.[5]

In animal experiments, tachyphylaxis has been demonstrated with veratridine and protoveratrine and, with the former, is related to the size of the dose, i.e., it develops less readily when the dose is at, or near, the minimal effective dose.[5] Freis and Stanton [2] observed tolerance in hypertensive patients treated with veratrum viride orally. Our studies showed no clear-cut evidence of the development of tolerance following intravenous admin-

istration of 0.2 c.c. of veratrum viride, repeated as often as every 24 hours, and given in some patients after they had already been subjected to tests of the effect of increasing doses well beyond the effective 0.2 c.c. dose. An exception was present in patient J. Pa., in whom repeated 0.2 c.c. doses, following dose acceleration studies, showed a gradually less effective depressor action. However, changes in the clinical course of a patient, both emotional and physical, often make it difficult to ascribe changes in reaction to the drug alone. It must be noted that during this phase of his study his basal blood pressure was rising, and he had become ambulatory and was preparing to leave the hospital.

The studies of the effect of dose acceleration indicated that 0.2 c.c. produced a maximal effect in most patients with a minimum of nausea and vomiting. If the patients were able to tolerate larger doses, the dose-effect curve showed a tendency to level off, with symptoms of nausea and vomiting finally appearing, before any evidence of vascular collapse. Nausea and vomiting thus appeared regularly when the drug dosage was carried high enough. However, in many patients an effective lowering of the blood pressure could be achieved without such effects, and the percentile fall in MBP bore no relationship to the occurrence of these symptoms. The subjective reactions described by all patients were similar; however, the development of nausea and vomiting appeared to depend on a variable individual threshold.

Freis has reported the absence of significant postural hypotension in his studies.[1] However, our results indicated that in a number of patients a postural effect was present following the administration of the drug which was at its maximum during the period of maximal drug action. This phenomenon was associated with a rise in pulse rate and a relative maintenance of diastolic blood pressure. Syncope was not noted as may occur following tetraethylammonium chloride.[9] One might assume that the neurogenic control of postural responses is maintained, or at least that any effect on it is transient as compared with the over-all depressor effect of veratrum.

Our results are in general in agreement with those of Meilman and Krayer, who employed protoveratrine, a pure alkaloid, in their studies. A variety of clinical types of hypertension was tested. Results similar to ours were observed as concerned the pulse changes, the effect of atropine, the effect of repeated doses, the influences of change in posture and the nature of subjective sensations. However, the incidence of nausea and vomiting was less. While the amount of protoveratrine which caused a given fall varied from patient to patient, their data do not indicate that type and severity of the disease had any relationship to the effective dose.[5]

Although we employed a mixture of alkaloids, it does not appear that the "impurity" of the preparation played any rôle in the variable individual sensitivity. The similarity of our results to those of Meilman and Krayer,

and the findings in recent studies in our laboratory on the comparative effects of the intravenous administration of three different veratrum preparations (Veratrone, Veriloid and protoveratrine), would seem to bear out this assumption.[5, 10]

Summary and Conclusions

The effect of intravenous administration of veratrum viride on blood pressure and pulse rate was studied in 38 hypertensive and 10 normotensive subjects.

The results demonstrated a similar depressor response to a fixed dose in both groups. Considerable variability of this response was exhibited within each group. The individual degree of response in the hypertensive patients could be correlated only with the initial diastolic pressure, in that patients with higher levels showed a significantly smaller percentile fall.

Symptoms of nausea and vomiting were present in one-third of the patients. They were unrelated to the percentile fall of blood pressure and were not diminished by simultaneous administration of atropine sulfate. However, atropine did prevent bradycardia without significantly affecting the depressor response.

Repeated interval injections of veratrum viride revealed no evidence of the development of tolerance in the blood pressure response. In addition, studies with doses of increasing size demonstrated a "leveling off" of the dose-effect curve, with the eventual appearance of nausea and vomiting as the limiting factor to further increase.

The studies bear out the ability of veratrum viride consistently to produce a fall in blood pressure, but emphasize the difficulty in determining individual responsiveness to the drug.

Acknowledgments

The authors are indebted to Dr. Samuel Rapoport, of the Research Foundation of the Children's Hospital, Cincinnati, Ohio, for his valuable guidance in the statistical analysis of these data.

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A COMPARATIVE STUDY OF THE EFFECTS OF VERATRUM VIRIDE AND TETRAETHYL-AMMONIUM CHLORIDE IN HYPERTENSION *

By ALVIN P. SHAPIRO, M.D., ALBERT A. BRUST, M.D.,† and EUGENE B. FERRIS, M.D., F.A.C.P., *Cincinnati, Ohio*

ASSALI, Brust et al. have recently reported a comparative study of the actions of veratrum viride (Veratrone) and tetraethylammonium chloride (TEAC) in normal and toxemic pregnancy. In all toxemic cases, the blood pressure remained elevated or fell only slightly following autonomic blockade with TEAC, but fell markedly with the intravenous administration of veratrum viride.[1]

Since such a consistent difference between the actions of the two drugs occurred in toxemia of pregnancy, it seemed worthwhile to carry out a similar study in patients with other types of hypertension.

MATERIAL AND METHODS

Fifteen hypertensive patients were studied; these included 11 with benign essential hypertension of varying degrees of severity, three with malignant hypertension and one with chronic pyelonephritis and hypertension. In one of the patients with malignant hypertension, the malignant phase was superimposed on previously existing chronic renal disease. They were part of a larger group of 38 hypertensive patients in whom the effects of intravenous administration of 0.2 c.c. of Veratrone were studied, and the material and methods for obtaining the data concerning the "Veratrone floor" have been reported.[2] TEAC † was given in a dose of 4 c.c. (400 mg.) an hour and a half to two hours prior to the Veratrone ‡ injection. The methods of TEAC administration and determination of the "TEAC floor" have been described by Brust, Assali et al.[3]

The procedure in these 15 patients was thus identical to that employed in the study of patients with toxemia, except for the use of atropine sulfate in doses of 0.8 mg. to 1.2 mg., along with the 0.2 c.c. dose of Veratrone. It has been shown that atropine administered simultaneously does not significantly alter the "Veratrone floor." [2]

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From the Hypertension Research Laboratory of the Department of Internal Medicine, College of Medicine, University of Cincinnati, Cincinnati General Hospital. This study was supported in part by a grant from the American Foundation for High Blood Pressure and the Life Insurance Medical Research Fund.

† Research Fellow, American Heart Association.

‡ Veratrone and tetraethylammonium chloride (Etamon) were supplied by Parke, Davis & Company through the courtesy of Dr. E. C. Vonderheide.

Results

The data concerning the paired TEAC and Veratrone responses are presented in table 1. The patients have been divided into two groups, one consisting of eight patients who showed a "low TEAC floor" (systolic and diastolic pressures below 150/100 mm. Hg), and the other of seven patients with a "high TEAC floor" (systolic and/or diastolic above 150/100 mm. Hg).

Table I

Comparison of Depressor Effects of TEAC and Veratrone

Name	Diagnosis*		TEAC				Veratrone			
			Initial Blood Pressure	TEAC Floor	Per cent Fall Syst. BP	Per cent Fall Diast. BP	Initial Blood Pressure	Veratrone Floor	Per cent Fall Syst. BP	Per cent Fall Diast. BP
			(Mm./Hg)				(Mm./Hg)			
			Low TEAC Floor							
A. H.	BEH		300/118	105/60	65.0	49.2	241/114	90/50	62.5	56.1
M. O.	BEH		228/122	145/85	35.7	30.4	220/118	166/96	24.5	18.6
J. H.	BEH		225/110	140/80	37.8	27.3	214/124	78/60	63.5	51.5
V. G.	BEH		187/115	130/80	25.2	30.4	171/110	115/70	32.7	36.3
L. Br.	BEH		183/116	134/86	26.8	25.9	190/119	118/86	38.0	27.6
C. L.	BEH		177/110	110/70	37.9	36.5	172/110	110/86	36.0	27.3
P. St.	MH		195/127	130/88	33.3	30.7	193/130	120/90	37.8	30.8
D. H.	MH		168/120	125/90	25.9	25.0	172/121	150/110	14.7	9.1
		Average			36.0	31.9			38.7	32.2
			High TEAC Floor							
D. T.	BEH		229/118	190/100	17.1	22.7	211/121	190/100	9.5	17.3
M. M.	BEH		223/142	175/120	21.5	15.5	200/135	150/115	25.0	16.1
E. D.	BEH		207/136	150/110	25.3	19.2	206/133	159/108	22.7	18.8
N. W.	BEH		184/125	165/120	10.3	4.0	196/131	170/125	13.2	4.6
Fa. J.	BEH		169/113	130/105	23.1	7.1	166/125	130/100	21.7	20.1
I. O'L.	MH		217/126	200/120	7.6	4.8	213/122	190/110	10.8	9.7
J. B.	CPN		198/120	175/116	11.6	3.3	193/124	166/112	14.0	9.7
		Average			16.6	10.9			16.7	13.8
		Average for all Patients			28.7	21.8			28.9	23.1

* BEH: Benign Essential Hypertension. MH: Malignant Hypertension. CPN: Chronic Pyelonephritis.

The group with "low TEAC floors" showed average systolic and diastolic percentile falls to TEAC of 36.0 per cent and 31.9 per cent, respectively. The corresponding percentile falls to Veratrone were 38.7 per cent and 32.2 per cent.

The group with "high TEAC floor" showed average systolic and diastolic percentile falls to TEAC of 16.6 per cent and 10.9 per cent respectively.

The corresponding percentile falls to Veratrone were 16.7 per cent and 13.8 per cent.

The average percentile falls for the entire group of 15 patients were 28.7 per cent systolic and 21.8 per cent diastolic with TEAC, and 28.9 per cent systolic and 23.1 per cent diastolic for Veratrone.

Discussion

The data indicate that the inverse relationship between the depressor effects of TEAC and veratrum viride, which is apparent in toxemia, is not evident in a random group of patients with hypertension of different etiology.

In toxemia, the difference in the actions of the two drugs indicated that, although the elevation of blood pressure is of humoral origin, as evidenced by its persistence after autonomic blockade, nevertheless these patients are responsive to veratrum viride.[3, 4] However, that the action of veratrum viride is not therefore a specific one on humoral mechanisms is borne out by the present study.

In this group, which includes patients with essential hypertension and chronic renal disease with associated hypertension, the magnitude of blood pressure response with the two drugs was similar. Maximal depressor action of veratrum viride was seen in patients with "low TEAC floors," in whom presumably the humoral contribution to blood pressure maintenance was small, while conversely, with greater humoral tone, as reflected in "high TEAC floors," veratrum viride had minimal effects. This evidence suggests that veratrum viride, rather than having any specific humoral effects, acts through producing vasodilatation whose effectiveness depends on the degree or severity of the peripheral resistance encountered,[2] regardless of the extent to which humoral, neurogenic or other mechanisms contribute.

Summary and Conclusions

The effects of intravenous administration of veratrum viride and TEAC were compared in 15 patients with hypertension. In contrast to toxemia of pregnancy, where the results of the two drugs are diametrically opposed (TEAC having little or no effect and veratrum viride producing a marked fall in blood pressure), these 15 patients showed a similar blood pressure fall to each drug when they were given on the same day.

The results support the concept that the vasodilatation produced by veratrum viride is not specific in terms of the various mechanisms interrelated in the maintenance of the elevated blood pressure, but depends on the degree or severity of peripheral resistance which is present.

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THE CHOICE OF PRECORDIAL LEADS IN THE DIAGNOSIS OF CORONARY ARTERY DISEASE*

By MAX POMERANCE, M.D., JULIAN B. HOFFMAN, M.D., and GEORGE J. ASHE, M.D., *Brooklyn, N. Y.*

RECENT progress in the clinical application of the electrocardiogram has led to its widespread usage by the general practitioner. In private practice the majority of doctors requesting cardiac consultation have taken the initial electrocardiogram. For these physicians, the choice of precordial leads has become a problem because of the listing of CF, V, CL and CR leads on the universal lead selector switch of the new electrocardiograph machines and the replacement of CF by V leads in many hospitals. The value of multiple precordial leads has been amply demonstrated.[1-4] The type of precordial lead, on the other hand, has been the subject of dispute for over a decade. In 1938 the joint British-American Cardiac Committee recommended CF leads for routine use.[5] Since then there has been an increasing volume of literature [1, 7-9] attesting to the supremacy of the unipolar (V) precordial leads. While it is true that Wilson,[6, 10] Myers [2, 3, 4, 11, 12] and Sokolow [13, 14] have established the accuracy of the V leads in myocardial infarction and ventricular hypertrophy, their superiority over CR and CF leads has not been universally accepted,[15, 16] nor has it been demonstrated that the V leads are most reliable in distinguishing cardiac and noncardiac pain. As a matter of fact, Wolferth and Livezey [15] and Wallace and Grossman [16] have objected to the routine use of V leads on theoretic and empiric grounds. Nevertheless, the trend in the literature and in practice appears to be in the direction of replacing CF leads by V leads.[1, 7] In a recent paper,[8] seven cases were reported as showing "false positive" CF findings because the V leads were negative, indicating that the V leads were accepted a priori as accurately reflecting the true state of the heart. In the past few months we have seen 12 instances, of which we wish to present six in detail, in which the CF leads have seemed to be more consistent with the clinical picture. These cases are cited not as an argument in favor of retaining CF leads for the routine electrocardiogram, but as examples of one condition in which the CF leads may be of more value than the V leads.

CASE REPORTS

Case 1. A 50 year old man was first seen on September 28, 1950, complaining of having had recurrent attacks of precordial pain for the past few months. The attacks occurred with effort and were relieved by rest. The chest pain radiated down the left arm.

* Received for publication May 11, 1951.
From the Department of Cardiology, Beth-El Hospital, Brooklyn, N. Y.

Past History: Moderate hypertension for two years.

Physical Examination: The patient was a sthenic adult in no distress. The blood pressure was 150/94 mm. of Hg. The heart was of normal size, the sounds of good quality and regular. The lungs were clear. There were no signs of congestive failure.

Fluoroscopy: The aorta was widened and knuckled; the heart was of normal size; the lungs were clear.

Course: The patient returned on November 9, feeling much better and reporting only occasional anginal pains on strenuous effort.

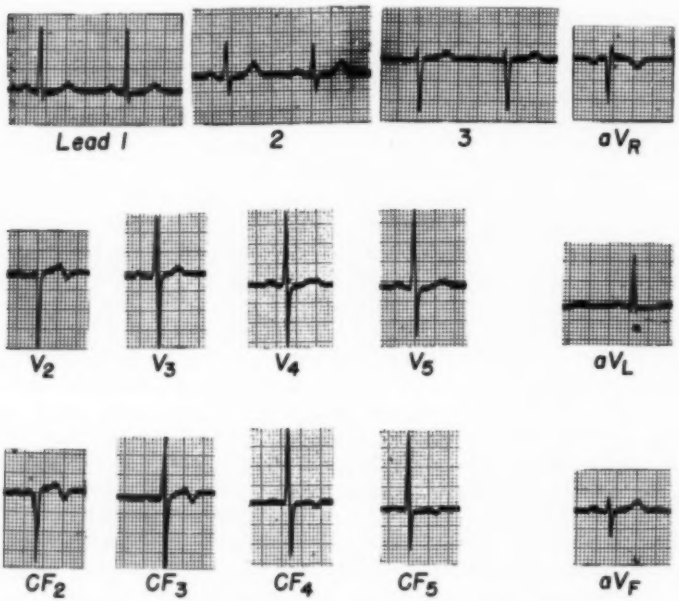

FIG. 1. *Case 1,* 50 year old man with angina pectoris. EKG, September 28, 1950: T in CF_2 through CF_5 mainly inverted. T in V chest leads (V_2 to V_6) upright. T_1 smaller than T_3. T_{aVL} flat and T_{aVF} upright.

*Electrocardiogram,** 9/28/50 (figure 1): T_1 smaller than T_3. T_{aVL} flat. T_{aVF} positive, T in V chest leads (V_3–V_5) upright. T in CF leads (CF_2–CF_5) inverted.* 11/9/50 (figure 2): Entirely normal. T_1 larger than T_3. T upright in CF leads and in aVL.

Comment: This patient presented symptoms of coronary artery disease, and the electrocardiographic findings in the precordial CF leads, as well as

* The method of recording was uniform in all the illustrated electrocardiograms; the patient's position was the same in each. The V precordial and CF leads were recorded alternately so that each numbered precordial lead (V_2 and CF_2, V_3 and CF_3, etc.) was obtained with the electrode at the identical place on the chest wall for CF and V.

conventional and unipolar limb leads, support the clinical impression. The initial V chest leads are therefore considered to show false-negative findings. The reversion of all electrocardiographic findings to normal with the subsidence of symptoms is not only consistent with the diagnosis of coronary artery disease but also actually confirmatory.

Case 2. A 49 year old man was seen on December 5, 1950, because of an attack of substernal pain experienced four days previously. The patient had first experienced substernal pain three weeks before, while walking; at that time the pain had lasted

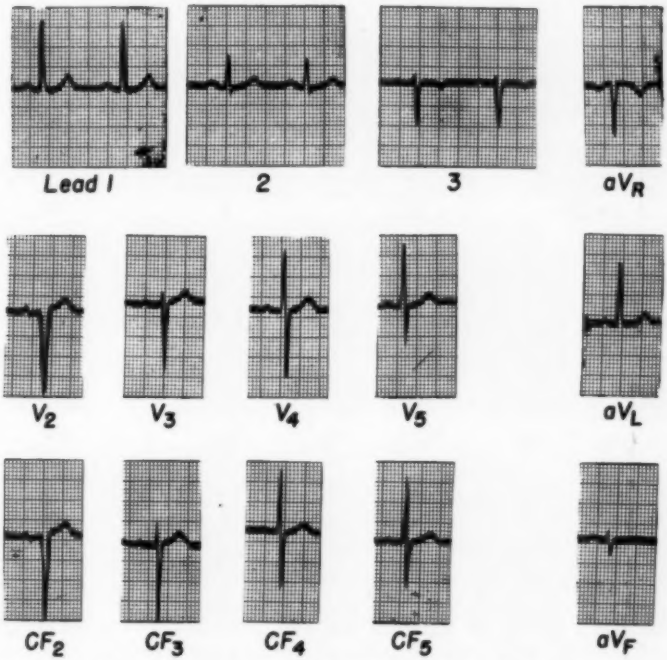

FIG. 2. *Case 1*, after subsidence of symptoms. EKG, November 9, 1950: Entirely normal. T upright in CF, V chest series and both limb series. T_1 larger than T_3.

20 minutes and was relieved by rest. The next day the patient had an attack at home which lasted all night. The pain radiated to both shoulders and down the left arm. Four days later while walking to the theater he experienced a similar attack, which was relieved by rest. Since then these anginal episodes had recurred frequently, the last on December 1.

The review of systems and past history were noncontributory.

Physical Examination: The patient was a well developed middle aged male in no distress. The blood pressure was 108/66 mm. of Hg. The entire examination, including the cardiorespiratory system, was normal.

Fluoroscopy: Heart and lungs were normal.
Electrocardiogram (using V precordial leads): Normal.
Impression: Angina pectoris.

Course: The patient was advised to rest at home for a period of observation. On December 19 he was seen again for a recurrence of substernal pain. A repeat electrocardiogram (figure 3) showed diphasic T waves of the plus-minus type, chiefly upright in V_2 and V_3, whereas T waves were clearly inverted in CF_1 to CF_4 and diphasic in CF_5. T_1 was smaller than T_3, T_{aVL} inverted, T_{aVF} upright. Following a period of restricted activity and clinical improvement, a repeat electrocardiogram (April 7, 1951, figure 4) was completely normal in both CF and V series (limb and chest leads).

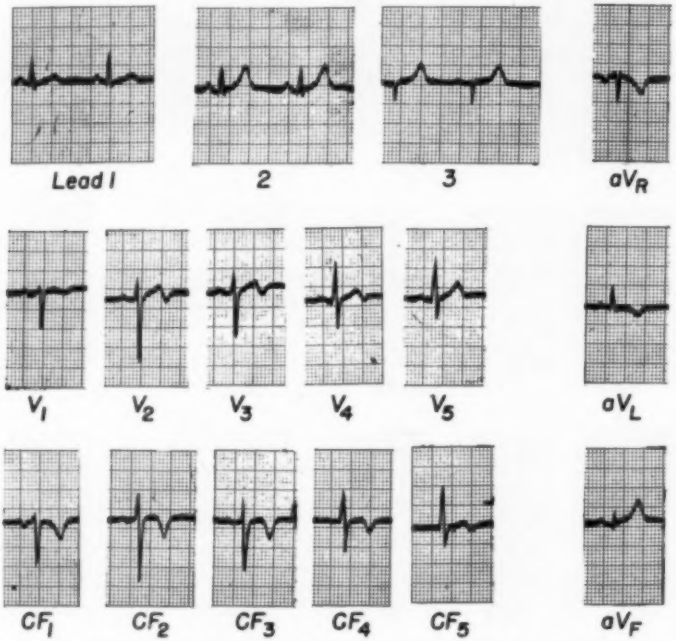

FIG. 3. *Case 2*, 56 year old man with angina pectoris. EKG, December 19, 1950: T in CF Leads I through IV inverted. T in CF_5 diphasic. T in V_2 and V_3 diphasic. V_4 and V_5 normal. T_{aVL} inverted, T_{aVF} upright. T_1 smaller than T_3.

Comment: Clinically, the patient has angina pectoris. The precordial CF leads and limb leads confirm this impression. The V chest leads were essentially normal, the changes being minimal in V_2 and V_3. The reversion of the electrocardiogram to normal in the limb leads and in both precordial series after subsidence of symptoms strongly supports the likelihood of a previous coronary episode.

Case 3. A 39 year old man was seen on December 12, 1950, because of recurrent precordial pain. One month previously, the patient had begun to experience precordial pain on walking and climbing stairs. The pain radiated down the left arm and was relieved by rest. On December 5 the patient had had a severe attack of chest pain, unrelated to exertion, which persisted for three hours. Since then, angina had recurred with effort to the time of examination.

The review of systems and past history were noncontributory.

Physical Examination revealed a well developed, normasthenic man in no distress. Blood pressure was 120/60 mm. of Hg. Heart was of normal size, the heart sounds

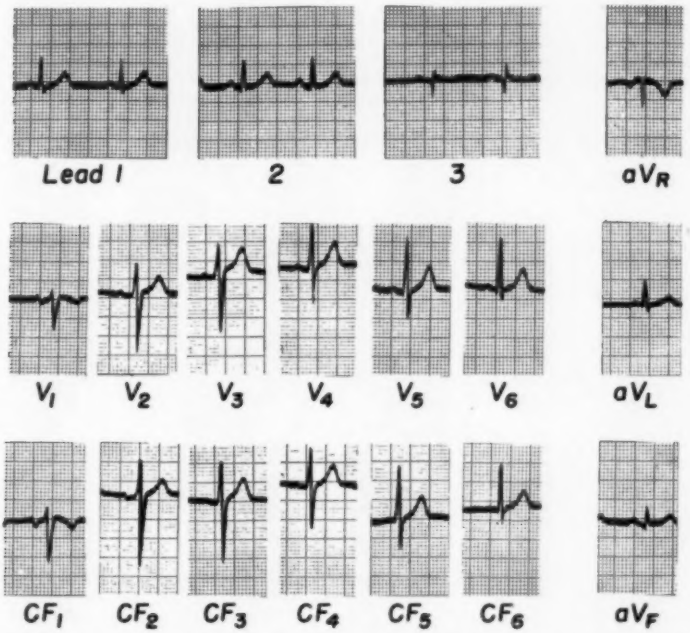

FIG. 4. *Case 2,* after bed-rest and relief of symptoms. EKG, April 7, 1951: Normal in both CF series and V series (chest and limb leads). T_1 larger than T_3.

were of good quality and regular, and there were no murmurs. The lungs were clear.

Fluoroscopy: Heart and lungs were normal.

Impression: Angina pectoris.

Electrocardiogram, 12/12/50 (figure 5): T_1 smaller than T_3. T_{aVL} inverted. T_{aVF} upright. T in precordial V leads (V_2–V_5) upright and T in CF leads (CF_2–CF_5) inverted.

Course: A repeat electrocardiogram on February 6, 1951 (figure 6), with CF and V chest and limb leads two months later, was entirely normal. A Master two-step test showed diagnostic ST depressions, however (figure 6: X_1 and XV_4).

Comment: This is a clear example of a case of angina pectoris and coronary heart disease in which the CF leads were diagnostic and the V leads falsely negative.

Case 4. A 44 year old man was admitted to Beth-El Hospital on July 1, 1950, with a history of recurrent chest pain for three weeks prior to admission. The pain was substernal and pressing, and radiated down the ulnar aspect of the left arm; it was relieved by rest. An electrocardiogram prior to admission was considered diagnostic of acute myocardial infarction.

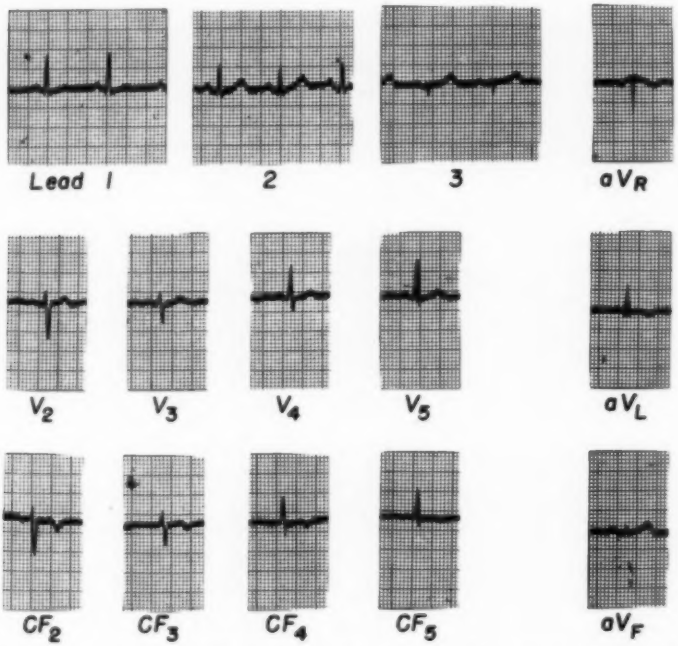

FIG. 5. *Case 3.* 39 year old man with angina pectoris and an episode of prolonged substernal pain. EKG, December 12, 1950: Normal except for T inversions in CF leads (CF_2 through CF_5). T upright in V chest leads (V_2 to V_5). T_1 smaller than T_3. T_{aVL} inverted, T_{aVF} upright.

The review of systems and past history were noncontributory.

Physical Examination: The patient was an obese male in no acute distress. The blood pressure was 110/86 mm. of Hg. The heart was not enlarged, the rate was 80 and the rhythm regular. There were no signs of cardiac decompensation.

Electrocardiogram: Serial electrocardiograms showed changes of an acute myocardial infarction (figure 7).

X-ray: Heart normal size; lungs clear.

Laboratory: The sedimentation rate was 10 mm. per hour on July 3 and 32 mm.

per hour on July 10. The white blood count on July 1 was 11,500, with 58 per cent segmented neutrophils.

Course: The patient was treated in routine fashion and made an uneventful recovery. The temperature reached 100.4° F. the fourth day of hospitalization but was otherwise unremarkable. The patient was discharged on July 30.

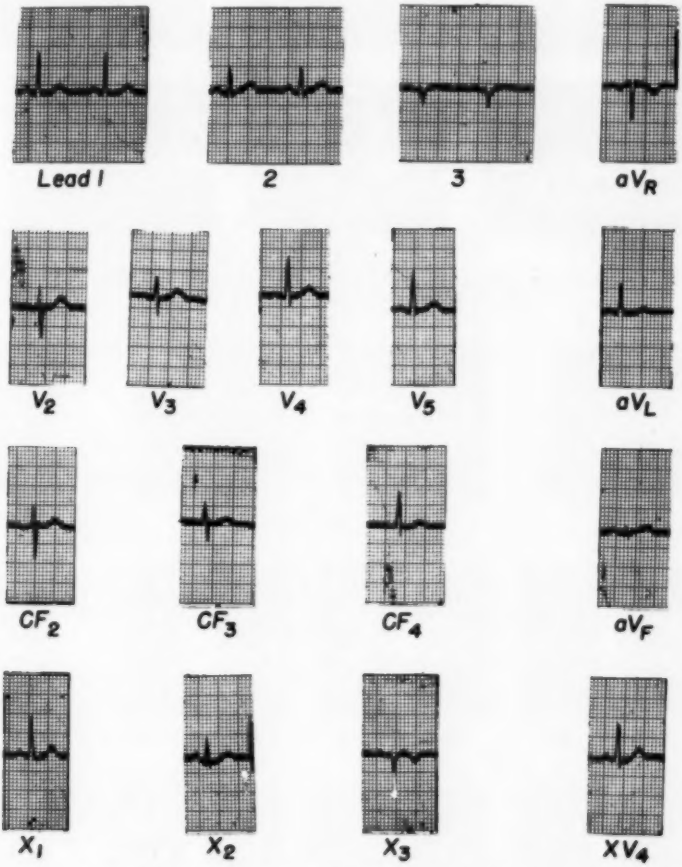

FIG. 6. *Case 3*, patient asymptomatic. EKG, February 6, 1951: Normal in CF and V series. Exercise tolerance test positive; ST depressed in X_1 and XV_4.

The patient was seen on March 31, 1951, for a routine check-up. Since discharge from the hospital the patient had had only a few mild anginal attacks.

Follow-up Electrocardiogram (figure 8) showed T_1 smaller than T_3, T_{aVL} inverted, T_{aVF} upright. T waves in V precordial leads show minimal abnormalities

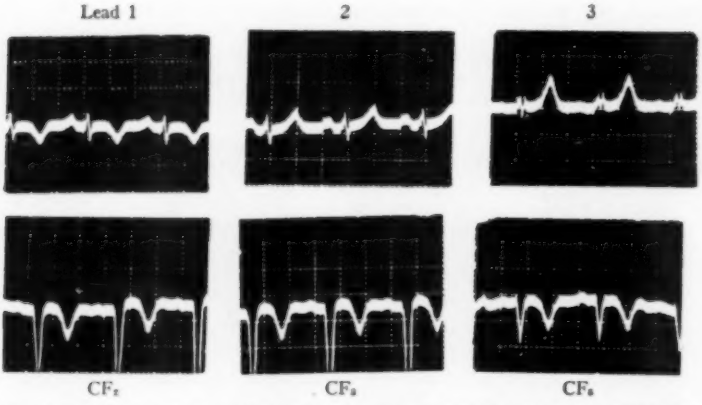

FIG. 7. *Case 4*, 44 year old man hospitalized for acute myocardial infarction. EKG, July 7, 1950: Acute anterior wall myocardial infarction.

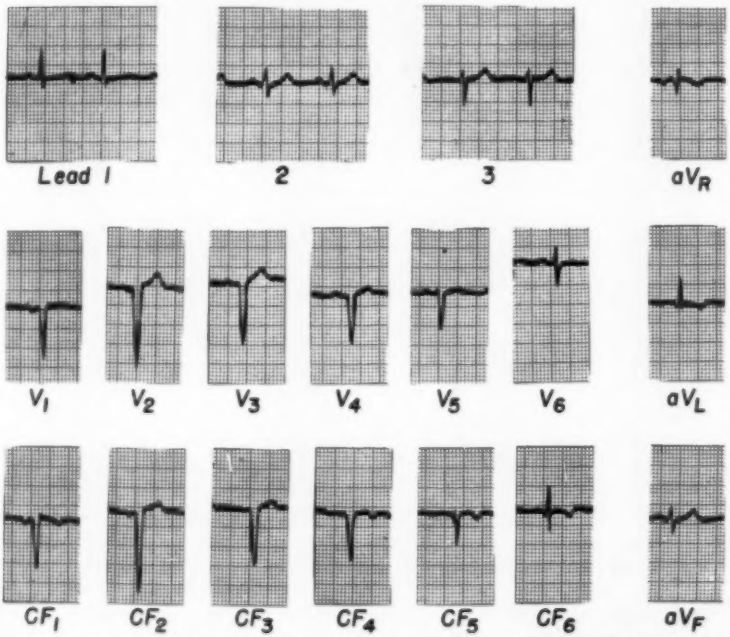

FIG. 8. *Case 4*, routine check-up six months later. EKG, March 31, 1951: T in CF_4–CF_6 clearly inverted. T in V_4 to V_6 low voltage and tendency to diphasism. QS in V_1 to V_4, CF_1–CF_4. T_1 smaller than T_3. T_{aVL} inverted, T_{aVF} upright.

in V_4 to V_6, with low voltage and a tendency towards diphasism. T waves in CF_4 to CF_6, on the other hand, are clearly inverted. QS is present up to the fourth precordial position. There is a small r in V_5 and a W shaped QRS in CF_5.

Comment: In this case the clearcut picture of myocardial infarction provides unequivocal evidence of myocardial damage due to coronary artery disease. Nevertheless, the difference in the follow-up electrocardiogram between the T waves in the CF and V precordial leads is as striking as in the three cases of angina presented above. While the QS in V_1-V_4 (figure 8) represents the previous anterior wall infarction, the T waves in the V chest leads (V_1-V_6) have all become upright; by contrast, the T waves in CF_4

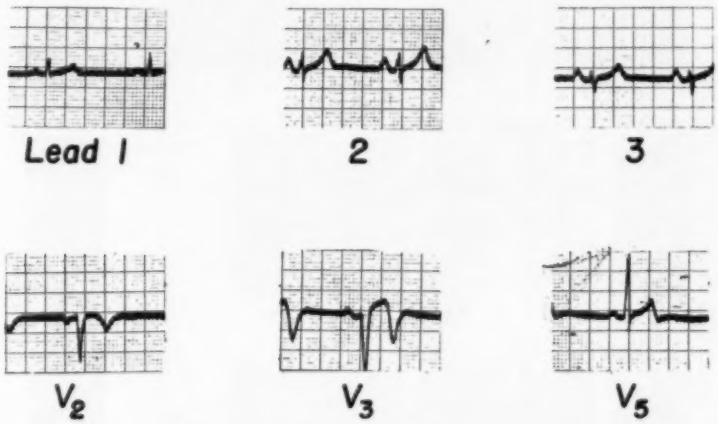

FIG. 9. *Case 5,* 56 year old man hospitalized for acute myocardial infarction. EKG, December 13, 1950: Acute anterior wall infarction.

through CF_6 are distinctly inverted. Thus, the T waves in the CF leads clearly identify the diffuse myocardial pathology which is not evident from the T waves in the V chest leads.

Case 5. A 56 year old male was admitted to Beth-El Hospital on November 29, 1950, because of persistent chest pain. The patient had been awakened from sleep the night before by severe substernal pain which lasted all night and was accompanied by cold sweats, pallor and numbness.

Physical Examination: The patient was a well developed, well nourished adult male in no distress. The blood pressure was 110/70 mm. Hg. Positive findings included a soft apical systolic murmur and dullness with decreased breath sounds at the left base, as well as fine moist râles.

Electrocardiogram (figure 9) revealed typical findings of an acute anterior myocardial infarction.

X-ray: Heart of normal size; aorta dilated.

Laboratory: The initial white blood count was 9,800, with 69 per cent segmented

neutrophils, 1 per cent staff forms, 30 per cent lymphocytes. The sedimentation rate was 18, rising to 26 at the end of the first week.

Course: The patient was treated in routine fashion and made an uneventful recovery. The temperature reached 100° F. on the fourth day of hospitalization.

The patient was reëxamined on March 10, 1951, for a routine checkup.

Follow-up Electrocardiogram (figure 10) showed T_1 smaller than T_3, T_{aVL} flat. T_{aVF} erect. T waves in V precordial leads are normal (diphasic V_4?). The T waves are diphasic in CF_2 and CF_3 and inverted in CF_1, CF_4, and CF_5.

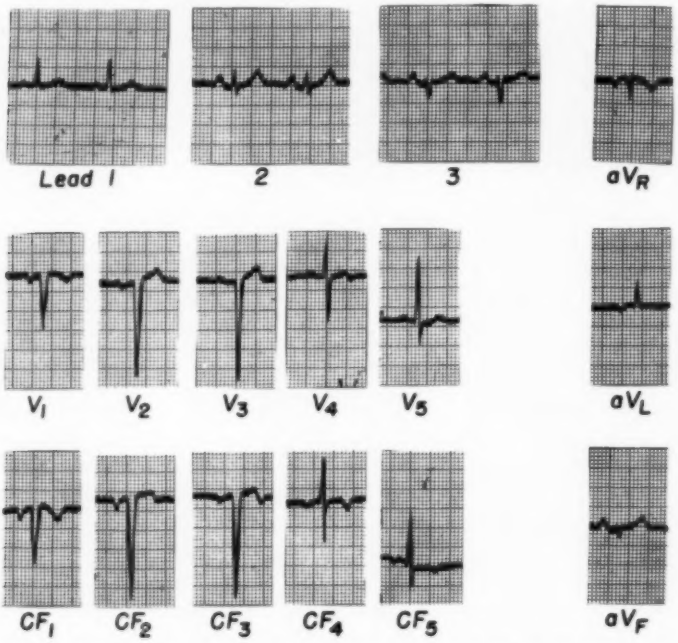

FIG. 10. *Case 5*, routine check-up six months later. EKG, March 10, 1951: T mainly inverted in CF_3–CF_5, T upright in V_3 through V_5. QS in V_1 to V_3 and CF_1 to CF_5. T_1 smaller than T_3, T_{aVL} inverted and T_{aVF} upright.

Comment: This case is similar to case 4. The patient had had a myocardial infarction in 1950. A repeat electrocardiogram three months later showed striking differences between the CF and V precordial leads. The latter may be considered within normal limits. The CF leads, on the other hand, definitely indicate extensive myocardial disease. The antecedent record of infarction substantiates the validity of the CF findings in identifying coronary artery disease.

Case 6. A 65 year old woman was hospitalized at Beth-El Hospital on February 21, 1949, for an acute myocardial infarction.

Physical Examination: The patient was a well developed, well nourished elderly female. The blood pressure was 156/80 mm. of Hg. The heart was not enlarged, the rhythm was regular and there were no murmurs. The lungs were clear.

Electrocardiogram showed acute myocardial infarction.

Course: The patient recovered and was discharged in five weeks.

The patient was re-admitted to Beth-El Hospital on April 7, 1951, with a history of recurrent attacks of chest pain which had begun six weeks prior to admission. The night before admission the patient had had a severe attack requiring morphine.

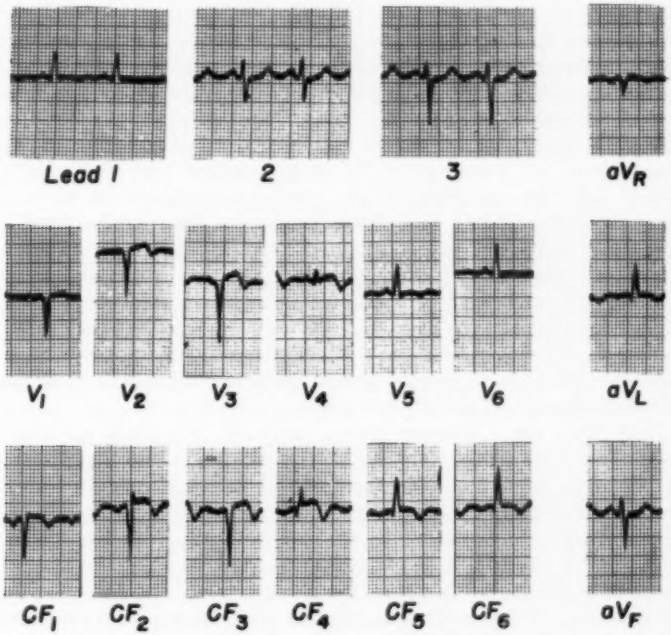

FIG. 11. *Case 6*, hospitalized for second myocardial infarction. EKG, April 7, 1951: Acute anterior wall infarction evident in both V and CF series. There are, however, high takeoffs in CF_3, CF_4 and CF_5, suggestive of a recent infarction; these are not evident in the V chest series. Two days later, EKG showed ST elevations in the V series indicative of acute infarction.

Follow-up Electrocardiogram (figure 11) showed T_1 smaller than T_3, T_{aVL} inverted, T_{aVF} upright; QS was present in V_1 to V_3, and QR in V_4. QS was present in CF_1 to CF_3, and QR in CF_4 to CF_6, with T wave inversions across the precordium in both V and CF leads.

Comment: In this case of proved infarction, both the CF and V precordial leads showed abnormal T waves across the precordium. It is of interest that there were ST elevations in CF_2 and CF_4, suggesting an acute process, confirmed in serial electrocardiograms, whereas there were no significant ST

elevations in the V leads in this electrocardiogram, although they did appear in a subsequent tracing. In several other cases, not included in this report, we have noted diagnostic changes occurring in CF leads one to three days before their appearance in the V chest leads. We are unable to offer an explanation of this phenomenon.

Discussion

With the progress in clinical electrocardiography, there has developed a growing volume of theoretic literature [6, 10, 15, 17] aiming to establish a rational basis for the clinical findings. The cornerstone of most electrocardiographic theory, of course, has been Einthoven's classic work, which has been confirmed (in the opinion of the majority of investigators) by mathematical analysis,[6] animal experimentation [18] and postmortem study.[19, 21] In the course of the past 25 years, Wilson and his group have contributed the bulk of the evidence [6, 10, 18] supporting the validity of the Einthoven triangle as a means of analyzing quantitatively the various elements of the electrocardiogram. In these studies it was demonstrated that the magnitude and direction of the P, QRS or T in any limb lead could be calculated from the values in the other two leads.[10] Although numerous experiments have been cited [10] confirming the validity of the Einthoven triangle, the evidence has not been universally accepted. Wolferth [18] and Katz [5] have presented data and theory rejecting the Einthoven concepts. It is not our intention to reëxamine this controversy, but we wish to observe that the genesis of the electrocardiogram is still disputed and its validity still empirical.

Based upon the Einthoven theory, unipolar (V) leads have been developed as a means of recording cardiac potentials semi-directly as the nearest approximation to direct leads from the heart surface itself. Most authors [1, 6-9] have accepted the value of the unipolar leads but, despite the plethora of theoretic confirmation, the validity of the V leads is not beyond question.[5, 15, 22] Wilson [10] himself has emphasized that he agrees with Einthoven that the application of the triangle to the calculation of cardiac potentials is only approximately true mathematically. Likewise, the unipolar lead of Wilson involves an approximation of the truth, since the central terminal may sometimes have a potential of as much as 0.3 millivolt during the cardiac cycle, rather than its theoretical value of 0. Thus the Wilson lead may at times be considered to be a bipolar lead. It is interesting in this connection to note the finding of Lowen and Pardee [23] in comparing the conventional bipolar limb leads with the augmented (Goldberger modification of the Wilson) leads. They found the conventional leads more frequently diagnostic of disease than the aV limb leads in the cases of posterior myocardial infarction and angina pectoris which they studied. It may be true, in a like manner, that the CF leads correspond more closely to the clinical picture in certain cases, although the V leads may be more accurate in recording cardiac potentials.

In the last analysis, it must be stated that electrocardiography remains clinically an empiric science. For this reason we must still be guided by clinical experience in evaluating the significance of electrocardiographic findings. This is particularly apropos in conditions like angina pectoris, where electrocardiographic findings are abnormal in only 50 per cent of the cases.[24] In three of the cases presented above (cases 1, 2 and 3), the problem was that of differentiating cardiac and noncardiac chest pain. Clinically, the patients had classic angina pectoris. In all three cases the V leads were normal and CF leads abnormal (T inverted in CF_2 to CF_5). Repeat electrocardiograms in cases 1 and 2 after clinical improvement showed reversion of CF and aVL leads to normal. In case 3, subsequent electrocardiograms showed reversion of CF and limb leads to normal, but, significantly, a Master test was positive! This was particularly convincing evidence of the validity of the CF findings in these cases.

In Kistin's article,[8] in which seven cases of "false positive" CF findings are reported, one of the cases had a positive Master test (case 5); one with substernal discomfort developed T wave changes after a Master test (case 6); one with precordial pain and thromboangiitis obliterans had low T in V_5 and V_6 leads (case 7); in one, T was inverted in V_3 and low in V_4 and V_5 (case 2); and in one with cerebral arteriosclerosis, T in V_5 and V_6 was flat and T_1 became inverted after the Master test (case 4). The statement is made in several of these cases that the diagnosis of heart disease was considered "but not thought likely." It is clear that in five patients heart disease was certainly not excluded, and it is therefore far from definite that the CF leads were inaccurate.

In the light of the reports by Ashman et al.[25] and Dressler [26] on the significance of T_1 being smaller than T_3, it is especially interesting to note that this phenomenon was present in all of our cases and all of Kistin's. In Ashman's series, 80 per cent of the cases had hypertensive heart disease when T_1 was smaller than T_3 and there was less than 30° right axis deviation. In Dressler's series of 45 cases, all had other electrocardiographic or clinical evidence of coronary artery disease; 36 had abnormalities in lead 4F. In nine cases, the only electrocardiographic corroboration of coronary artery disease was that T_1 was smaller than T_3. In his discussion, Dressler notes the occasional occurrence of these changes in vertical hearts as emphasized by Eidikin and Wolferth, but he points out that this is accompanied by right axis deviation of the QRS as well. In a subsequent article [27] on the subject of T_1 being smaller than T_3 Dressler and Roessler conclude: "Whenever the pattern is observed in cases presenting a history of sudden onset or aggravation of anginal pain it should strongly suggest an ischemic myocardial lesion." When pulmonary emphysema and vertical heart are ruled out, they consider the pattern T_1 smaller than T_3 is equivalent to the T_1 type of myocardial infarction "in the great majority of cases." None of the cases we are reporting had vertical hearts.

In our cases and Kistin's we have noted several other distinctive electrocardiographic features. Not only was T_1 smaller than T_3, but T was flat or inverted in aVL and upright in aVF. In Sokolow's study of 150 normal cases,[28] he found that T in aVL was never negative when R in aVL was greater than 5 mm. In all of our cases, R was 5 mm. or more. In our three cases (cases 1, 2 and 3) in which the T waves in the CF leads and aVL reverted to normal, there was no change in the QRS. This indicates that there was no alteration in the electrical axis but that the T wave changes were primary, representing a change in the state of the myocardium, and were not merely secondary to rotational changes.

Three of our patients had been previously hospitalized with classic clinical and electrocardiographic findings of myocardial infarction. The V precordial leads in a recent electrocardiogram in one (case 5) gave no definite indication of myocardial disease. The CF leads, on the other hand, give clear evidence of diffuse myocardial pathology (figure 10). In a recent electrocardiogram in another (case 4), QS is present in V_1 to V_3 but the T waves are upright. In V_4 to V_6 the ventricular complexes are rS and the T waves are diphasic. The CF leads, by contrast, clearly indicate extensive old anterior wall infarction! In the third patient (case 6), both V and CF leads revealed previous diffuse anterior myocardial infarction. The CF leads suggested acute changes several days earlier than the V chest leads.

Because of our experience in these cases, we have begun to record CF and V chest leads in all cases in which the limb leads show T_1 smaller than T_3. If this finding accompanies an inverted T in aVL and an upright T in aVF, we anticipate abnormal T waves in the CF leads and suspect cardiac pathology, provided the heart is not vertical, regardless of the findings in the V precordial leads. We have reported one case in which T wave inversions are seen in the CF and V chest leads. The point we wish to emphasize, however, is that in all of our cases the CF leads have been unmistakably abnormal, whereas the V precordial leads usually were not diagnostic.

In none of the cases fulfilling the electrocardiographic criteria described above did the V chest leads uncover pathology missed by the CF leads.

Summary and Conclusions

Six cases with coronary artery disease are presented in which the CF leads appear to be more consistent with the clinical findings than the V chest leads. Three cases gave a history of angina pectoris and three had documented evidence of previous myocardial infarction. In one case, T waves were abnormal in both the CF and V chest leads. It is of interest that the conventional and the unipolar limb leads also showed a distinctive pattern in that T_1 was smaller than T_3, T_{aVL} was flat or inverted and T_{aVF} was upright. With subsidence of symptoms in the cases of angina, the abnormalities in the CF leads disappeared. T_1 became larger than T_3, and T_{aVL} became upright, while there was no change in the electrical axis of the heart.

The three cases with proved myocardial infarction serve to corroborate our impression that the CF findings, in the presence of the electrocardiographic pattern described in the limb leads, indicate myocardial pathology (in these cases due to coronary artery disease), despite the negative V chest leads.

In a dozen cases which we have recently seen, the CF leads have always shown negative T waves in the presence of T_1 smaller than T_3, T_{aVL} negative and T_{aVF} positive. The V chest leads have also shown negative T waves in some cases. Frequently, however, the CF leads were abnormal and the V leads normal, whereas the reverse situation was not encountered. In several cases of infarction (not reported) in which both CF and V series showed abnormalities, the changes in the CF series either occurred one to three days earlier or were far more distinctive.

It is recommended that when T_1 is smaller than T_3, T_{aVL} is negative, and T_{aVF} is positive, provided R_{aVL} is 5 mm. or more, CF leads be done in addition to V leads.

While it is recognized that there is a strong theoretic basis for the greater accuracy of the V leads as an indication of the potential of the subjacent myocardium, it is emphasized that the accepted electrocardiographic interpretations are primarily empiric. It is therefore reasonable to expect, as has been the case in this series, that the CF leads may sometimes indicate myocardial abnormality when the V leads (chest) apparently do not do so.

Addendum

Since this article was submitted for publication, the senior author has encountered 18 additional cases with features similar to those described in the text.

Acknowledgment

We wish to acknowledge our thanks to Dr. Harold E. B. Pardee for his aid in reviewing this manuscript.

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DIFFUSE INTERSTITIAL FIBROSIS OF THE LUNGS*

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In 1944 Hamman and Rich [1] reported the histories and autopsy findings of four patients whose disease was characterized by a relatively sudden onset of dyspnea, cough, cyanosis and fever, and early signs of cardiac decompensation. Death resulted within a short time of acute pulmonary suffocation or heart failure. The lungs at autopsy revealed diffuse interstitial fibrotic changes of a type which the authors had never seen previously. They were unable to find any similar cases reported in the literature, with the exception of one instance of interstitial pulmonary fibrosis associated with lesions of periarteritis nodosa, by Kneeland and Smetana.[2]

In 1945 Eder and associates [3] published the fifth instance of acute interstitial fibrosis of the lungs. We have found reports of eight additional cases with postmortem confirmation which, in the opinion of the authors, duplicated the disease described by Hamman and Rich, making in all 13 cases.[4-9] In a study of pulmonary patterns of pulmonary fibrosis as related to pulmonary function, Spain [10] tabulated data on seven cases with diffuse interstitial pneumonia with fibrosis, several of which probably fell into the group described by Hamman and Rich. But the description of the individual cases is too meager to permit inclusion in the present series.

The following is an additional instance of diffuse interstitial fibrosis of the lungs of the type described by the authors mentioned. We are prompted to make a detailed review of the subject because it is our impression that, once the condition is recognized, it may prove less rare than is generally believed and not so acutely progressive as has been found in most of the cases reported to date.

Case Report

A 44 year old female secretary, married 10 years but childless, had been brought up as a foster child, her father having died of pulmonary tuberculosis at the age of 40 and her mother of cancer at the age of 40. Through a foster child medical service, the patient was frequently examined during her childhood and early adult life. Repeated x-ray examinations of the chest had shown no evidence of disease. From 1927 until the time of death, the patient had been under the care of one physician (D. P.). She was seen frequently because of a chronic persistent cough. In 1934, the patient had an appendectomy; in 1938, at the age of 32, she had her menopause and at about that time became prematurely gray. On June 26, 1947, she had a routine x-ray of the chest at the New York City Department of Health which was reported "negative."

In the spring of 1948 the patient noted shortness of breath on exertion and swelling of the ankles. The cough, which had always been dry, now became productive of small amounts of thick mucus; her appetite was good, and there was no

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loss of weight. The patient was admitted to the Lebanon Hospital on June 6, 1948. Examination disclosed a rather obese, stubby woman in no discomfort except for dyspnea on exertion. The only sign elicited on physical examination was the presence of râles in the left lower lobe. X-ray examination of the chest showed an exaggeration of the pulmonary markings throughout both lungs. The markings were more prominent in the left basal region and were ascribed to congestive changes (figure 1). Electrocardiogram showed "myocardial damage"; no evidence of right ventricular strain. Blood Wassermann test, negative; blood sugar, 80 mg. per cent; urea nitrogen, 9 mg. per cent; hemoglobin, 14 gm.; white blood cells, 8,400, with a normal differential; urine, negative. The sputum failed to reveal acid-fast organisms or fungi. The patient was given one injection of 2 c.c. Mercuhydrin and was discharged four days later with a diagnosis of "chronic bronchitis and coronary insufficiency."

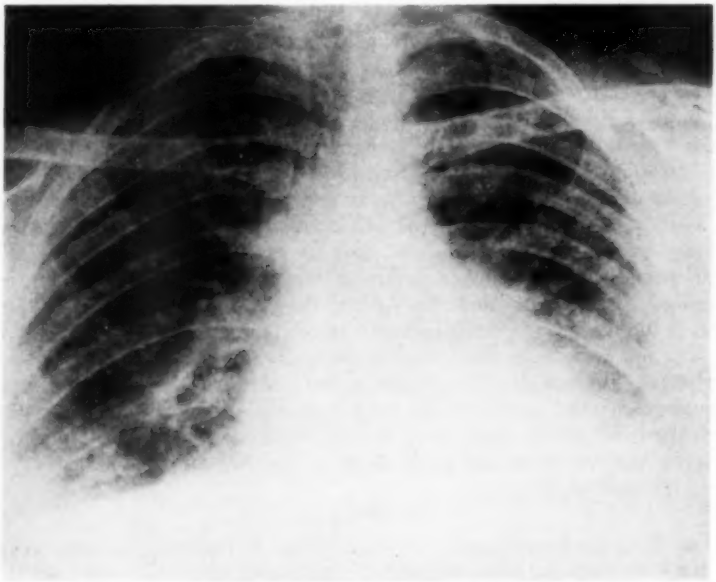

FIG. 1. Chest x-ray, June 20, 1949. Diffuse reticular infiltrations in both lungs; accentuation of hilar markings; enlarged cardiac shadow.

The patient continued to have cough and increasing dyspnea. On November 2, 1948, she was referred to one of the authors (E. H. R.). At this time her major complaints were cough, worse at night, moderate expectoration, palpitation, backache, dyspnea on exertion and two-pillow orthopnea. She stated that she occasionally had swollen ankles. The physical examination was noncontributory except for the finding of diffuse wheezing râles in both lungs, more numerous at the left base. X-ray examination of the chest revealed irregular accentuation of markings at both hilar regions and diffuse striations radiating throughout both lung fields, chiefly the left lower. In places the striations assumed a patchy configuration. There was slight pleural reaction at both bases. The outline of the cardiac silhouette was indistinct,

especially on the left side. The only additional findings on examination at this time were the elicitation of a rough systolic murmur at the mitral area and accentuation of P_2. The sedimentation velocity of the blood was 55 per cent in one hour (10 per cent for healthy adult female with method used). A provisional diagnosis of sarcoidosis was made. For the balance of 1948, the patient continued to be under the care of her private physician and from time to time received Mercuhydrin injections.

Because of increasing severity of cough, dyspnea and wheezing, she was admitted to the Montefiore Hospital on February 17, 1949, for additional study. The physical findings revealed nothing of additional significance. The blood pressure was 120/80 mm. of Hg. X-ray of the chest revealed findings almost identical with those previously described. X-rays of the hands and feet revealed no cystic changes. Laboratory examinations revealed total protein, 7.1 per cent; albumin, 4 per cent; globulin, 3.1 per cent; calcium, 10.2 mg. per 100 c.c.; inorganic PO_4 2.5 mg. per 100 c.c.; Mazzini test, negative; blood counts and urine, within normal limits. Repeated examinations of the sputum failed to reveal acid-fast organisms. Decholin circulation time, 35 seconds; venous pressure, 90 mm. While in the hospital, the patient received calciferol, 50,000 units three times a day. She was discharged March 6, 1949, her condition unchanged.

She continued under the care of her private physician until November 1949, when she registered at the Lebanon Diagnostic Clinic for additional studies. The symptoms were increasing dyspnea even at rest, two- to three-pillow orthopnea and considerable cough during the day, worse at bedtime. The physical examination now revealed a palpable liver, but otherwise the findings were as on previous occasions. An x-ray examination of the chest showed the same markings radiating throughout both pulmonary fields, the cardiac shadow being partially obscured by the infiltration; also, slight enlargement of the heart. An electrocardiogram taken on November 14, 1949, showed an inverted T in Lead II and Lead IV, suggestive of myocardial damage. Other laboratory tests were noncontributory. The patient reacted to tuberculin, .01 mg. O.T., and was strongly positive to 1 mg. O.T. At the suggestion of Dr. L. Siltzbach, a Nickerson-Kveim test was done, which proved negative.

On November 26, 1949, she was readmitted to the Lebanon Hospital because of sudden onset of fever to 101° F., increased dyspnea and cough. A bronchoscopy was done, and a biopsy and smears were taken for tumor cells. Except for inflammation of bronchial mucosa, no significant findings were obtained. Repeated examinations of the chest showed no changes. Roentgenograms of the pelvis and skull revealed no abnormalities. Additional laboratory tests were noninformative. Because of the marked dyspnea, the patient was given oxygen by mask or tent and after a period of 10 days improved sufficiently to be discharged.

She was readmitted to Lebanon Hospital on September 20, 1950, with the complaint that in the preceding year she had become short of breath to a point where she was unable to move around her apartment without effort. She had been treated with digitalis and Mercuhydrin, without effect. On admission to the hospital she was immediately placed in an oxygen tent and given supportive measures. Examination of the chest at this time disclosed râles throughout both lungs, more on the left. The liver edge was not palpable. The blood pressure was 110/70 mm. of Hg; pulse, 120. Respirations ranged from 40 to 60. X-rays of the chest revealed an increase in the infiltrations in both lungs, which now assumed a more nodular appearance and, in places, coalescence (figure 2). Electrocardiogram revealed signs suggestive of myocardial disease and right ventricular strain. An extensive series of tests was done at this time, but none gave any significant findings. The total proteins were 7.3 per cent; albumin, 3.1 per cent; globulin, 4.2 per cent. The blood count revealed white blood cells, 7,600, with a normal differential. Carbon dioxide com-

bining power of the blood, 68 vol. per cent; blood sugar, 118; urea, 16. The sputum was reëxamined for acid-fast bacilli and fungi and found negative.

The patient was given a trial of cortisone, 100 mg. daily, without improvement. She also received 250 mg. of aureomycin every four hours for a period of 10 days. The only measure that gave her some relief was continuous oxygen administration, either by mask or tent. About a week before death, she called attention to the presence of several hard lumps in both thighs. The temperature throughout this period ranged between 100° and 102.6° F. She left the hospital on October 13, 1950, only slightly improved. The final diagnosis was pulmonary fibrosis, etiology unknown. Four days later, she died rather suddenly with symptoms of acute respiratory failure. The body was removed to the Lebanon Hospital for autopsy. It might

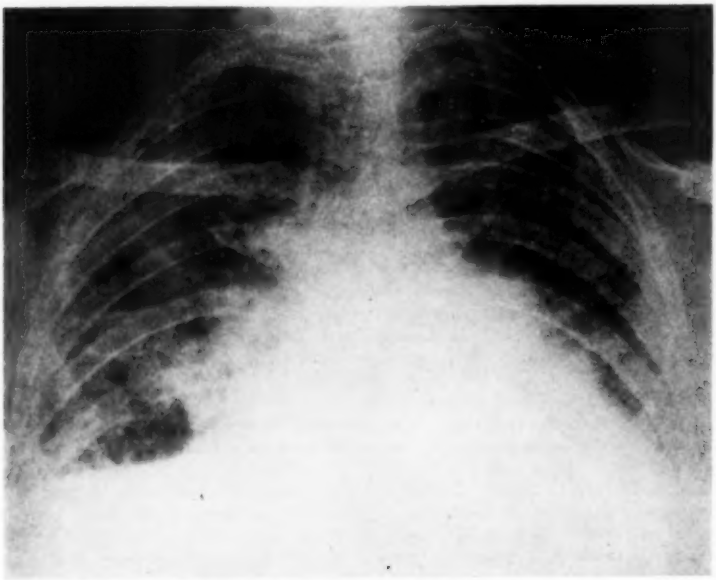

FIG. 2. Chest x-ray, October 2, 1950. Increase in infiltrations and hilar markings; conglomerate density in right lung.

be mentioned that, from the manner of her death more than from the course of the disease, it was suspected (before the autopsy findings were available) that the patient had interstitial fibrosis of the lungs of the type described by Hamman and Rich.

Report of Necropsy (Joseph C. Ehrlich, M.D.)

General Description: The body was that of a well developed, well nourished middle-aged white female weighing approximately 140 pounds and measuring 5 feet in length. There was no rigor mortis and the body was still warm. The color of the skin was a light tan. There were prominent veins over the upper anterior chest. On the extremities there were several ecchymoses at the site of needle puncture marks. The visible mucous membranes were pale and faintly cyanotic. The pupils were

round and equal. The teeth were in a good state of repair. There was no peripheral lymphadenopathy. The breasts were flabby and contained no abnormal masses. The abdomen was soft and showed striae. There was a right paramedian scar, 15 cm. long. The fingers and toes were clubbed. The panniculus adiposus was well preserved. In both thighs anteriorly and laterally, ill-defined nodular subcutaneous masses were felt. These were located in the subcutaneous fat tissue and consisted of dense gray-red infiltrations, varying in size from a pea to several centimeters in diameter. They were distinctly demarcated from the glistening yellow normal fat tissue.

Body Cavities: Peritoneal: There were fibrous adhesions of the omentum to the abdominal scar. The peritoneal surfaces were smooth and glistening, and there was no fluid in the peritoneal cavity. The domes of the diaphragm were high, reaching the third interspace on the right side, the fourth on the left side. The liver and spleen were hidden beneath the costal arches. Pleural: The pleural cavities did not contain excess fluid, and there were no pleural adhesions. Pericardial: There were a few cubic centimeters of clear, straw-colored fluid in the pericardial sac.

Cardiovascular System: The heart weighed 245 gm. The myocardium had a normal red color and was firm. There was no gross evidence of fibrosis or softening. The right ventricle was 2 to 3 mm. in thickness. There was a dilatation of the pulmonary conus of the right ventricle and of the left atrium. The myocardium of the left ventricle was 1 cm. in thickness. There were two small nodules, 3 to 4 mm. in diameter, on the atrial surface of the posterior leaflet of the mitral valve. They were firm and had a granular surface and broke off readily, leaving a small area of roughening on the valve. The remaining endocardium was not unusual. The pulmonary and aortic rings measured 6.5 cm. in circumference. The mitral ring measured 7.5 cm. in circumference, whereas the tricuspid ring measured 8 cm. The coronary ostia were patent. The descending branch of the left circumflex was occluded by a red thrombus 2 cm. long. The inferior vena cava and its tributaries were strikingly engorged. The aorta showed occasional atheromatous plaques.

Respiratory System: The lungs were reduced in size, their general configuration being preserved (figure 3). They held their shape on the table and were heavier than normal, the right weighing 580 gm. and the left 430 gm. The pleura showed occasional patches of dullness with small fibrinous deposits, particularly in the interlobar fissures. There were no pleural adhesions. The overall color of the lung surface was purple. On closer inspection, a considerable irregularity of color and structure of the surface was discerned. The interlobular septa were widened and depressed, leaving between them slightly elevated nodular portions which appeared to have a lobular distribution; these had a lighter tan color, contrasting with the purplish-gray or black of the retracted portions. In places there were larger, flat, somewhat depressed areas which were smooth and gray; beneath these areas the lung tissue was very firm. The lungs were noncrepitant, and palpation revealed a diffuse, ill-defined, nodular, rubbery consistency. Section through the pulmonary parenchyma revealed complete loss of the normal feathery structure of lung tissue (figure 4). It was for the most part transformed into a finely honey-combed and granular substance which had a dull red-brown color. This altered lung tissue was subdivided into patchy areas of varying size and shape by branching, thickened gray septa. In places there were more extensive, solid, smooth gray portions which were completely airless and firmer than the remaining lung substance. While a small amount of air was present in most of the right lung and in the left upper lobe, the left lower lobe was completely airless and markedly reduced in size. On section it showed extensive fibrosis and consolidation of lung tissue and very prominent bronchial and vascular markings. The color of the tissues in this lobe was dark gray. The lingula of the left upper lobe was also firm and completely airless. On section it showed a nodular

FIG. 3. Left lung, unfixed specimen. Pleural surface shows accentuation of interlobular septa and nodularity.

gray infiltration which appeared to follow the distribution of the bronchi, some of which were dilated, others completely obliterated. The nodules averaged 1 mm. in diameter. The intervening lung tissue was partly dark red, partly gray with anthracotic pigment, and solid. Immediately under the pleura there were occasional blebs up to 5 mm. in diameter, the lining of which was thick and opaque. The remainder of the lungs showed somewhat less prominent bronchial and vascular structures. The medium sized bronchi had thick walls, and their lumen was filled with a thick, brown mucoid material. The trachea and main bronchi were empty; their mucosa was pale

and showed very delicate granularity. The large branches of the pulmonary artery were dilated; their intima was smooth. The hilar and paratracheal lymph nodes were enlarged, succulent and dark purple. On section they showed small patches of pale gray color within the purple or black parenchyma.

Nothing remarkable to bear on the case was found in the liver, spleen, pancreas, urinary system, genital system, endocrine system, lymphatics, bone or brain substance.

FIG. 4. Left lung, unfixed specimen. Cut section shows rigid organ, finely honeycombed pattern in upper lobe and large area of consolidation in apex of lower lobe.

Histopathologic Findings: Lung: Twenty-four sections of lung from different lobes were examined. These were prepared with various stains, including hematoxylin and eosin, elastica Van Gieson, Mallory, trichrome, Sudan and Gram stains. The following is a general description covering the essential histopathologic changes in all of these sections. *Pleura:* The pleura was uninvolved in almost all of the sections studied. The pathologic alterations in the parenchyma of the lung appeared to stop just short of the pleura itself. *Septa:* The septa in which the major vessels run appeared to be involved by the pathologic process. They presented increased vascularity, increased connective tissue, and infiltration by numerous inflammatory cells, chiefly round cells and plasma cells. *Arteries:* The various subdivisions of the pulmonary arterial tree showed thickening extending down into the smallest branches; most of the changes appeared in the intima and media. The vessels were hypertrophied, and there was marked subendothelial fibrous thickening. Similar changes were found in many of the veins. There were occasional thrombi present in small subdivisions of the pulmonary veins. *Lymphatics:* No significant changes. *Nerves:* No significant changes. *Bronchial tree:* In the small subdivisions of the bronchi, the smooth muscle appeared hypertrophied. Many of the bronchi contained mucus and occasionally blood. Occasional leukocytes and exfoliated alveolar lining cells occurred in bronchial lumina. *Tracheobronchial lymph nodes:* Central area of pigmentation and scarring. *Paratracheal lymph nodes:* Moderate nonspecific hyperplasia. *Hilar lymph nodes:* Moderate nonspecific hyperplasia, with focal pigmentation. One section of lymph node showed extensive hyalinization, with a few foci of secondary calcification.

Alveoli: The main pathologic findings were in the alveolar elements of the lungs (figures 5 and 6). The involvement was patchy, so that the parenchyma appeared solid in some areas and permeated by air spaces in others. In many of the solid areas the alveoli contained fresh fibrin and numerous erythrocytes (figure 6). In all sections the alveolar walls were strikingly thickened (figures 5 and 6). They were lined by cells that appeared to be markedly hypertrophied and occasionally somewhat atypical alveolar lining cells, usually in a single layer and occasionally stratified. In a few foci, squamous metaplasia was observed (figure 7). In characteristic areas the thickening of the alveolar walls presented the appearance of an active granulomatous process. Between the two layers of hypertrophied alveolar lining cells there was an increase in ground substance and an increase in the number of fibroblasts; the capillaries appeared somewhat compressed, and there were numerous inflammatory cells, particularly round cells and occasionally plasma cells. In many alveoli the hypertrophied lining cells presented the appearance of pseudoglands. Frequently the cellular infiltrate was more abundant and included polynuclear leukocytes. Stains for bacteria were negative. Elastic tissue stains brought out the vascular thickening. There was no significant increase in the elastic tissues in the alveolar walls; fibrils of elastic tissue were separated by ground substance and collagen. Fat stains showed clusters of macrophages, with intracytoplasmic fat droplets in some of the alveolar lumina. The alveolar lining cells were negative for fat. The granulomatous interstitial tissue contained occasional fat laden macrophages. There was no histologic evidence of lipoid pneumonia or abnormal lipids. There were scattered areas of intra-alveolar pneumonic exudate, predominantly polynuclear leukocytes, fibrin and erythrocytes. The pneumonic exudate showed no tendency toward fibrous organization. Many alveoli were lined by "hyaline" membranes.

Heart: Left ventricle—a few tiny fibrous scars. Slight fiber hypertrophy. One perivascular scar of the "combed-out" type. Papillary muscle—fiber hypertrophy. Right ventricle—interstitial infiltration by fat. One periarterial collection of plump Anitschkow cells. Septum—moderate subendocardial fibrosis.

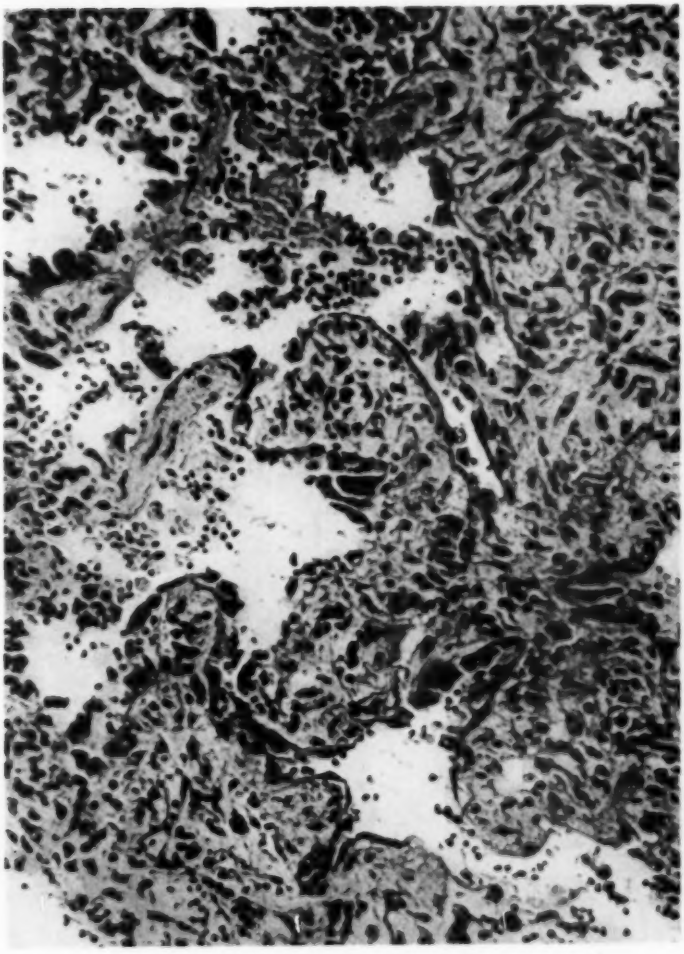

FIG. 5. Photomicrograph. Section shows marked thickening of alveolar septa due to proliferation of fibroblasts and cellular elements; alveolar capillaries compressed; prominence of alveolar lining cells.

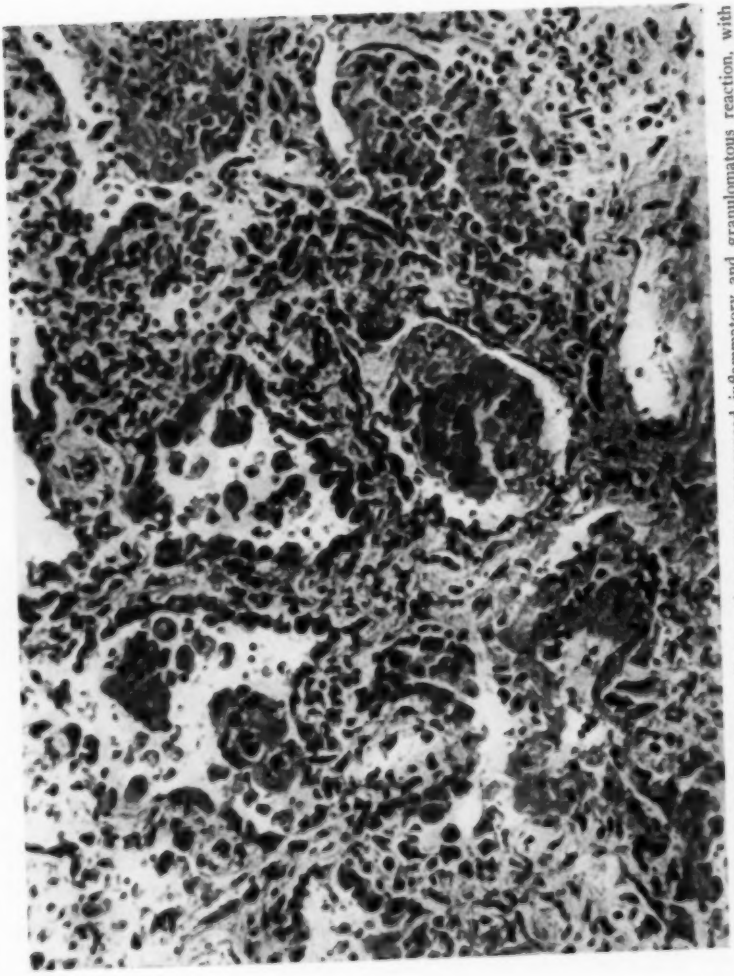

FIG. 6. Photomicrograph. Section shows more pronounced inflammatory and granulomatous reaction, with exudation of fibrin, macrophages and round cells; alveolar lining cells show pronounced metaplasia, giving a pseudoglandular appearance.

FIG. 7. Photomicrograph. Section shows completely fibrosed area with chronic inflammatory reaction; squamous metaplasia of bronchiolar epithelium.

Histologic examination of the remaining organs revealed no significant abnormalities.

Anatomic Diagnosis: 1. Diffuse interstitial fibrosis of the lungs. Focal fibrinous pleuritis. Inflammatory hyperplasia of hilar lymph nodes. 2. Dilatation and hypertrophy of right ventricle, pulmonary artery and left atrium (cor pulmonale). Congestion of vena cava and tributaries. Recent occlusion of left circumflex coronary artery. Endocardiosis of mitral valve. 3. Fatty changes of liver. 4. Subcutaneous fat necrosis of both lower extremities (secondary to therapeutic needle puncture). 5. Infantile uterus. Atrophy of ovaries. 6. Status 18 years after appendectomy.

Reported Cases

Case 1 (Hamman and Rich). In a period of three weeks a 47 year old colored male developed cough, dyspnea and swelling of the ankles. Nineteen years previously he had had pneumonia, from which he recovered; gonorrhea, and probably syphilis at an early age. He had been well and working until the present illness. On admission to the hospital he had moderate respiratory distress, brassy cough, a small amount of sputum and temperature to 101.4° F. Physical examination revealed engorged neck veins, harsh breath sounds and numerous fine and coarse râles; systolic murmur at apex; blood pressure, 130/100 mm. of Hg; liver enlarged. Laboratory examinations revealed Wassermann test positive; no acid-fast bacilli in sputum or fluid; abdominal aspiration revealed transudate; urine contained large amounts of albumin. Roentgenogram of the chest revealed dilatation of the heart and infiltrations of both lungs, at times suggestive of chronic passive congestion; at other times, miliary infiltrations suggestive of tuberculosis. The patient was treated with digitalis with diminution of the edema; temperature remained elevated; later, marked ascites and generalized anasarca, extreme cyanosis, increasing dyspnea, edema and delirium. Death by heart failure about four months after onset of illness. Postmortem examination revealed both lungs covered by extensive fibrous adhesions; fine, weblike interstitial diffuse fibrosis, with focal areas of emphysema associated with the scars. Microscopic examination showed interlacing bands of fibrous tissue, in places hyalinized; numerous mononuclear cells and scattering of eosinophils; cardiac enlargement confined to right side.

Case 2 (Hamman and Rich). A 21 year old colored female became ill with increasing dyspnea, chest pain, slight cough, fever and signs of heart failure. Pelvic operation 10 months previously; treated for syphilis and for elevated blood pressure. On admission to the hospital the patient was poorly nourished; temperature, 101° F.; blood pressure, 165/110 mm. of Hg; cough, expectoration, chest pain. Physical examination revealed areas of consolidation in left lung; later, also in right lung. Laboratory examinations revealed no growth on blood cultures; sputum negative for acid-fast bacilli; blood count not remarkable. Roentgenogram of the chest revealed large areas of consolidation of both lungs, suggestive of edema in association with pneumonia. Shortly after admission to the hospital the patient became desperately ill with cyanosis, delirium and dyspnea; recovered somewhat, but dyspnea increased and she died 46 days from onset of symptoms. Postmortem examination revealed both lower lobes occupied by gray, pinkish, red areas of considerable size. Microscopic examination showed a decided tendency to formation of a thick hyaline membrane of inspissated fibrin, and remarkable proliferation of connective tissue within alveolar walls; heart showed hypertrophy of right ventricle.

Case 3 (Hamman and Rich). A 37 year old colored female became ill with pain in the back and loss of weight. The patient had been treated for syphilis, and for hemoptysis one year previously. On admission to the hospital the patient was well nourished but in extreme dyspnea. There were moderate cyanosis, seizures of rapid,

shallow breathing, at times a picture of prostration and exhaustion, and gradual increase of expectoration and cyanosis. Laboratory examinations: acid-fast organisms in the sputum on two occasions. The initial white blood count was normal but later reached 17,800. Roentgenograms of the chest showed extensive infiltrations in both lungs, probably due to an old tuberculosis. There were progressive signs of consolidation of both lungs disproportionate to the extreme dyspnea. Postmortem examination revealed both lungs diffusely involved in a process of fibrosis. In addition, there was a localized tuberculous cavity in the left upper lobe which appeared unrelated to the diffuse fibrosis. Microscopic examination showed thickening of alveolar walls with a hyaline membrane, and many eosinophils. The heart revealed dilatation and hypertrophy of the right ventricle.

Case 4 (Hamman and Rich). A 68 year old white female developed dyspnea, cough and generalized malaise. She was treated for hyperthyroidism at the age of 19. On admission to the hospital the patient was undernourished. There was a slight elevation of temperature; later, a higher temperature with chills and cough, but little expectoration. Physical examination showed signs of progressive consolidation in both lungs. Roentgenograms of the chest revealed extensive infiltrations in both lungs, chiefly the right. Her course in the hospital was characterized by increasing dyspnea and prostration. Fluid aspirated from the right chest was found sterile on culture. She died six months after the onset of her acute illness. Postmortem examination revealed both lungs to be edematous, and scattered throughout all the lobes were translucent, firm gray areas. Microscopic examination showed diffuse thickening of the alveolar walls; lining of the alveolar cells greatly enlarged and hyaline membranes plentiful; fluid in both pleural cavities. The heart revealed nothing remarkable.

Case 5 (Eder et al.). A 47 year old white male became ill with cough, dyspnea, loss of weight and chest pain. On admission to the hospital the patient appeared thin, dyspneic and slightly cyanotic. Physical examination revealed transient râles in the right axilla. Late in the disease, a pleural friction rub was heard. Clubbing of the fingers and toes was also noted. Laboratory examinations: sterile blood cultures; other findings noninformative. Roentgenograms of the chest revealed extensive fine mottling in both lungs, most marked in the upper lobes, suggestive of miliary tuberculosis. The heart appeared enlarged. The patient's course in the hospital was characterized by gradual rise in temperature, increasing dyspnea, cyanosis and later severe air hunger; excruciating pain in the legs with absent pulsations in the dorsalis pedis arteries. The patient died of respiratory failure eight days after admission and approximately four months after the onset of acute symptoms. Postmortem examination revealed, on cut section of the lungs, a mosaic appearance of diffuse fibrosis, with interposed areas of emphysema as well as areas of pneumonic consolidation. Microscopic examination showed extensive interstitial fibrosis of both lungs, and alveolar walls greatly thickened by recently formed connective tissue. The right ventricle was appreciably hypertrophied. In addition, there were occlusion of the right iliac artery by an adherent thrombus and fresh infarcts in both kidneys.

Case 6 (Potter and Gerber). A 33 year old white male became ill, with tiredness and loss of weight and, later, cough, dyspnea and palpitation. On admission to the hospital the patient had moderate dyspnea, cyanosis and a raspy unproductive cough. Physical examination revealed scattered râles in both lungs. Laboratory examinations revealed nothing significant. Roentgenograms of the chest revealed initially a peculiar haziness over the lower third of both pulmonary fields; later, a progression of the process, which gave a veiled appearance to the lungs. The patient's course in the hospital was characterized by rise in temperature, increasing dyspnea and extreme cyanosis. The patient died of pulmonary insufficiency 32 weeks after the onset of the acute symptoms. Postmortem examination revealed both lungs

to be grayish-red and smooth, with accentuation of lobular markings. Microscopic examination showed pronounced thickening of alveolar septa due to varying degrees of connective tissue proliferation; also, striking proliferation of alveolar epithelial cells. There were marked hypertrophy and dilatation of the right ventricle and auricle.

Case 7 (Beams and Harmos). A 32 year old male became ill with cough and shortness of breath of three months' duration; there was occasional blood-streaked sputum. Physical examination was noninformative. Roentgenograms of the chest revealed findings characteristic of atypical pneumonia but, in view of lack of change in comparative films, it was considered due to a chronic infection producing pulmonary fibrosis. The film revealed streaky, fine mottled shadows in both lung bases involving the lower half of the left lung and the extreme base of the right lung. Laboratory examinations were non-informative. The patient's course in the hospital was characterized by cough, increasing dyspnea and, later, cyanosis, clubbing of the fingers, polycythemia and development of cor pulmonale. Death occurred 15 months after onset of illness. Postmortem examinations revealed in both upper lobes a uniform pneumonic consolidation, deep red on cut section, with frequent areas of emphysema and blebs enclosed by interlacing dense fibrotic tissue. Microscopic examination showed widespread interstitial fibrosis. Strips of fibrinohyaline membranes were conspicuous in or about alveoli. There was also marked proliferation of connective tissue in and about alveolar walls. There were hypertrophy and dilatation of the right ventricle.

Case 8 (Peabody and Hayes).* A 44 year old female became ill with cough, hemoptysis and exertional dyspnea. There was a striking paucity of physical findings. Roentgen examination revealed bilateral apical densities of a granular appearance suggestive of tuberculosis. Later films showed progression of process, the appearance now more in keeping with chronic interstitial pulmonary fibrosis. Laboratory examinations were noninformative; sputum was negative for acid-fast organisms. After a period of symptomatic improvement there was a return of severe cough and blood-streaked sputum, cyanosis, precordial pain and increasing dyspnea and cyanosis. Patient died of chronic suffocation three and one-half years after the onset of the disease. Postmortem examination revealed both lungs on section to be red and fleshy. Microscopic examination showed nearly all the alveoli replaced by dense hyalinized connective tissue; intervening stroma was fibrotic and diffusely infiltrated by chronic inflammatory cells. Heart was negative.

Case 9 (Ferrar et al.). A 63 year old female gave a two-month history of dyspnea, dry cough and cyanosis. Roentgenograms of the chest showed generalized, irregular mottling throughout both lung fields. The patient's course was steadily downward and she died of respiratory insufficiency four months after the onset of the disease. Postmortem examination revealed dense, carnified lungs with apparently normal pleurae. Histologically, the interstitial tissue was strikingly thickened by very young, vascular granulation tissue composed predominantly of fibroblasts but containing other cellular elements. This tissue invaded and encroached upon the alveolar spaces, areas of endothelial hyperplasia and metaplasia to the stratified squamous type of epithelium. In the involved areas the elastic fibers were almost completely absent, and several areas of bronchiectasis were noted. Some areas of the lung maintained a normal architecture and others showed emphysema.

Case 10 (Ferrar et al.). A 41 year old male had cough for several years. In the preceding years he had noted dyspnea, increased cough and expectoration of

* A twin sister with a similar pulmonary disease subsequently died and autopsy revealed identical pathological findings (MacMillan, J. M.: Familial pulmonary fibrosis, Dis. of Chest **20**: 426, 1951).

mucopurulent sputum, and weight loss. Roentgenograms of the chest showed multiple disseminated nodular shadows in both lung fields, more marked in the basal portions. The patient's course was rapidly downward, with cyanosis and progressive dyspnea. The patient died of respiratory insufficiency two months after admission to the hospital. Postmortem examination showed changes very similar to those of the preceding case. However, the degree of bronchiectasis was much more marked, and the arteries showed in some cases considerable reduction of the lumen as a result of intimal proliferation. The main pathologic picture was a striking interstitial proliferation of young granulation tissue.

Case 11 (Peabody, Moersch and Edwards). A 47 year old female had severe progressive dyspnea over a two-year period, accompanied by cyanosis and clubbing of the fingers. The pathologic features consisted of thickening of the alveolar walls by interstitial edema, increased number of capillaries, the presence of plasma cells and eosinophils, and proliferation of fibrous tissue. There were enlargement and metaplasia of the alveolar lining cells, an alveolar hyaline membrane, necrosis and desquamation of bronchiolar epithelium and focal organization of intraalveolar exudate. Microscopic examination of the lungs revealed the number of functioning alveoli to be less than one-half of normal, with marked thickening of the alveolar walls. The authors felt that this case represented a distinct anatomic picture and fit into the category of diffuse interstitial fibrosis described by Hamman and Rich.

Case 12 (Golden and Tullis). A 41 year old white male had cough, dyspnea, cyanosis and edema of the lower extremities developing over a period of years. There was a past history of recurring pneumonia and pleurisy. On admission to the hospital he had moderate dyspnea, cyanosis of skin and mucous membranes, and wheezing râles over both lungs; the heart was enlarged, and there were slight edema of the abdominal wall and moderate edema of the lower extremities, and definite clubbing of the fingers. Laboratory examinations: hemoglobin, 18 gm. per 100 ml. blood; red blood cells, 7,370,000; gradual increase in non-protein nitrogen. Roentgenograms of the chest showed marked reticulation, evenly distributed in both lungs. The heart was enlarged, with prominent pulmonary conus. During the hospital stay the patient had transitory episodes of marked cyanosis and dyspnea, with mental clouding. Venesection on two occasions had no effect on the condition. Death occurred on the twenty-first day of hospitalization, during an episode of dyspnea and cyanosis. Postmortem examination revealed extensive fibrous adhesions in both pleural cavities. Section of the lung revealed diffuse fibrous texture, between which tiny lobules of spongy lung tissue could be identified. Microscopic examination revealed interstitial fibrosis with thickening of alveolar septa, interlobular septa and peribronchial and peribronchiolar tissue. The medium and small branches of the bronchial tree were moderately enlarged, with peribronchial fibrosis interpreted as a mild subacute bronchiectasis. There was hypertrophy of the right ventricle.

Case 13 (Golden and Tullis). A 42 year old colored female developed over a period of nine months weakness and increasing dyspnea on exertion, swelling of the feet and increasing orthopnea. On admission to the hospital temperature reached 101° F., and there were râles over both lung fields. Laboratory examinations were noncontributory. In the hospital the patient had increasing fever and edema. Postmortem examination revealed in both lungs a picture of widespread, patchy fibrosis characterized by transformation of the spongy lung tissue to that of minute bands of interlacing scarring. Microscopic examination revealed a much wider distribution of interstitial fibrosis than was obvious grossly. An organizing pneumonia of lobular distribution was also present. The right ventricle was hypertrophied and moderately dilated. No significant valvular defects or myocardial lesions or coronary artery disease.

Summary of Reported Cases

The 14 cases of diffuse interstitial fibrosis of the lungs included in this paper comprise six men and eight women ranging in age from 21 to 68 years. Outstanding among the symptoms were cough, variable degrees of expectoration, occasional hemoptysis, chest pain, fever, increasing dyspnea and cyanosis. In a few the onset was insidious; in most, it was acute, even explosive. With the appearance of dyspnea and signs of heart failure, the course became rapidly downward, death occurring either of suffocation or, if the patient lived long enough, cardiac decompensation. The shortest duration of life from the onset of the final illness was 31 days; the longest, three and a half years. The physical signs relating to the pulmonary disease, as well as the laboratory findings, were in the main noninformative. A marked disproportion between objective findings and symptoms was often noted. Clubbing of the fingers and toes was noted in several cases, including our own. The roentgen findings also were not distinctive. A frequent occurrence was the presence of miliary, nodular or mottled infiltrations, involving diffusely both lungs and often associated with conglomerate areas of consolidation and occasionally pleural effusion, especially toward the end of life. In addition, there was usually cardiac enlargement.

The differential diagnoses variously entertained included tuberculosis, atypical pneumonia, chronic pulmonary infection, pulmonary edema associated with organizing pneumonia or cardiac disease, inhalational diseases and pulmonary manifestations of systemic diseases, such as blood dyscrasias, amyloidosis and allergic conditions, as well as metastatic neoplasm. In the case studied by the writers, the roentgenographic appearances suggested sarcoidosis. In all instances, the postmortem findings were of a fairly uniform pattern. The picture was that of a diffuse interstitial fibrosis of both lungs, with thickening of the alveolar septa, the latter being replaced by varying degrees of hyalinized connective tissue. The progressive nature of the disease was supported by the presence of different stages of development of the fibrotic reaction in various parts of the lungs. In almost every instance there was associated cardiac enlargement confined to or chiefly affecting the right heart.

Discussion

There has been much speculation as to the etiology of diffuse interstitial pulmonary fibrosis of the type described in these pages. Hamman and Rich [1] mention influenzal pneumonia and chemical irritants, as well as hypersensitivity to various agents, as possible causes. On the basis of their own experience, they conclude that either a virus or a chemical irritant might have been responsible. The several authors reporting instances of interstitial pulmonary fibrosis have little to add to the etiology of the disease. From a study of the individual protocols, one is impressed with the fact that the condition behaves like a pneumonia. Histologically, the picture resembles

influenzal pneumonia, with a characteristic alveolar hyaline membrane in many cases.[11] Allen and Spitz [12] found a marked degree of interstitial pneumonitis in scrub typhus and other rickettsial diseases which was indistinguishable from that of "Q" fever, rheumatic fever, toxoplasmosis and viral pneumonia. Tumulty, Berthrong and Harvey [13] reported three instances of a peculiar pneumonia in the course of which the patients developed progressive pulmonary insufficiency. An interesting feature was the presence of cytoid bodies in the retinae. The clinical and pathologic findings were suggestive of a virus pneumonitis with widespread fibrous organization of the lungs. Golden and Tullis [6] suspected that interstitial pulmonary fibrosis may be due to failure of resolution following one or more attacks of acute interstitial pneumonitis ("primary atypical pneumonia").

The disease evolves in slow stages over a period of months or even years. In the latter it may cause diffuse fibrosis involving not only the interstitial tissues but also the entire organ, including bronchi and blood vessels. The two cases reported by Ferrar,[5] as well as one described by Golden and Tullis,[6] had, in addition to interstitial fibrosis, variable degrees of bronchiectasis. Bronchiolar involvement was also noted in the four cases described by Hamman and Rich,[1] in one by Peabody and Hayes [8] and in several other instances. Involvement of blood vessels was also noted, the changes consisting of mild to severe intimal thickening of the arteries, and at times obliteration of the lumina. But it is difficult to state whether the vascular changes were part of the disease or secondary to the hypertension of the lesser circulation, which in time led to cor pulmonale in many cases. When significant degrees of emphysema, bronchiectasis and/or vascular damage are associated with diffuse interstitial pulmonary fibrosis, as we have had occasion to see in a number of instances,[14] the picture assumes a somewhat different pattern and the disease loses many of its "classic" features. But it is not improbable that the same causative agent or agents are responsible for all the changes noted. The degree and type of tissue response of the various components of the lung may vary in different individuals.

There is reason to believe that not all instances of diffuse interstitial fibrosis of the lungs of the type described are necessarily fatal. Inasmuch as the diagnosis can be proved only by histologic study of tissues obtained at autopsy, it is impossible to determine whether this supposition is correct. One of the writers (E. H. R.) had occasion to have an exploratory thoracotomy done and a biopsy of a lung taken in a 60 year old female whose course of disease and roentgen findings were highly suggestive of diffuse interstitial pulmonary fibrosis. The histologic picture was in keeping. We have learned, however, not to place complete dependence on a lung biopsy, so that the final diagnosis is still sub judice.

Summary

The case is reported of a 44 year old female who had diffuse interstitial fibrosis of the lungs of the type described by Hamman and Rich. A review of the literature reveals reports of 13 additional instances. It is postulated that the disease is caused by a virus and that the particular pathologic features represent one form of tissue response to a disease which may be associated with more widespread involvement. It is suspected that recovery may take place, but this cannot be proved since the diagnosis depends on a complete autopsy.

Acknowledgment

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HEMOPNEUMOTHORAX: REËVALUATION OF TREATMENT *

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SPONTANEOUS pneumothorax is relatively common, but its complication by hemorrhage is thought to be unusual. The problem of spontaneous hemopneumothorax has been well reviewed in the literature.[1, 2, 3, 4, 5, 6, 7] A recent article by Dorset and Terry [1] surveys 54 cases, 14 of which were fatal and had necropsies. Of the fatalities, 11 were dead within 24 hours. One death occurred 36 days later. At autopsy, from 1 to 4.5 liters of blood were found in the chest cavities. Relatively few clots were present. The source of bleeding was located in half of the cases. Five had torn pleural adhesions. It was not clear how many had fibrin on the pleural surface which would have prevented subsequent expansion of the lungs. The patients were in general treated according to the routine outlined by Hartzell.[4] This consisted of early removal of enough blood for diagnostic purposes, and more complete removal of blood if mediastinal displacement embarrassed the circulation or caused distressing dyspnea. Hartzell preferred delayed removal of blood, and suggested injection of air to maintain the pneumothorax and to prevent a too sudden alteration of the intrapleural pressure. He treated shock by transfusions. He suggested also that, if bleeding continued, surgery might be attempted to find a bleeding point, but he found no report of operative treatment in his comprehensive review of the literature. Dorset and Terry agree with Hartzell's outline of treatment and suggest, in addition, that after the first few critical days, aspiration of 200 to 500 c.c. of blood be done every few days, with partial replacement of the fluid by air.

War experience with cases of traumatic hemothorax has demonstrated the inadequacies of conservative management.[8, 9, 10] This is well summarized by Moore.[8] The method of choice is aspiration alone, "with a view toward emptying the pleura as quickly and completely as possible." The injection of air is condemned as being unnecessary and harmful.

Pneumothorax will not control bleeding from the chest wall. Bleeding from the lung is seldom a problem, because of the low pressure in the pulmonary circulation. War experience demonstrated that the "incidence of chronic hemothorax and chronic empyema is higher in those patients treated by aspiration and air replacement than in those treated by aspiration alone."

Simpson [11] feels that, in hemopneumothorax, the combined aspiration of apical air and basilar blood is the best method of insuring lung reëxpansion. Nalls and Matthews [6] also confirm our impression that the injection

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of air to maintain pneumothorax and "control bleeding" is irrational in spontaneous hemopneumothorax.

Therapy with aspiration alone may also be deficient, because of clotted blood and the resulting fibrothorax. The reason for clot formation in some cases and not in others has never been clear. It is especially interesting to see reports of cases with apparently massive bleeding who recovered with little or no withdrawal of blood. We cannot explain these variations in outcome with either similar or different modes of treatment. Although the value of pulmonary decortication weeks after a spontaneous hemopneumothorax to free an entrapped lung has not been emphasized in the literature, a recent article by Nalls and Matthews [6] stressed its importance in one of their cases.

The mortality figures for spontaneous hemopneumothorax, which have been reported as between 20 and 25 per cent, indicate that this is a very serious condition. If the patient has massive bleeding, the routine conservative treatment outlined above may not suffice. In the presence of massive bleeding with frequent aspirations, many transfusions will be necessary to maintain the patient's circulating blood volume and prevent shock. This can develop into a critical clinical situation. The following reports will demonstrate that, in such cases, immediate thoracotomy may have definite value both in the control of bleeding and in the prevention of fibrothorax.

The following cases were seen on the Chest Service of the Memorial Hospital between August, 1947, and December, 1950, and are presented in chronologic order.

Case Reports

Case 1 (previously reported [2]). A 27 year old man had massive bleeding several days following a spontaneous pneumothorax. The bleeding was severe enough in the first five days to require 4,000 c.c. of blood by transfusion to control shock and anemia; in the first nine days 6,465 c.c. of very bloody pleural fluid were removed from the right chest. The patient was acutely ill and several times appeared to be in immediate danger. In spite of frequent aspirations of blood, clots developed in the thoracic cavity; about a month after the initial pneumothorax, it was necessary to decorticate the lung. Eleven days of discomfort and hospitalization followed, and the patient was unable to return to work for another four weeks.

Case 2. A 26 year old man who had been treated conservatively for spontaneous hemopneumothorax was referred to the Chest Service a month or so later because of left anterior chest pain and dyspnea. His original x-rays showed that his pneumothorax was complicated by only minimal bleeding, which was not aspirated.

Thoracotomy revealed a fibrinous membrane holding the left lower lobe in complete collapse. The lower lobe was decorticated and reëxpanded. The outcome was only partially successful. Although this patient probably should have had blood aspirated initially, this case seemed to point out that even a small amount of bleeding may necessitate subsequent thoracotomy for decortication. This is notable because some authors [5] have maintained that aspiration of blood is not always necessary.

Case 3 (previously reported [13]). This 33 year old man was admitted to the hospital with the chief complaint of severe pain in the left chest beneath the scapula. The pain had begun two hours previously, when the patient turned in his desk chair at his office. Almost immediately he had developed dyspnea and became pale and shocked.

He had had a productive cough for three days. At the time of admission, the patient was found to be apprehensive and in acute distress. Respirations were 32 and were labored. There was intense chest pain upon movement of the body. Temperature was normal. Blood pressure was 150/102 mm. of Hg; pulse, 92. Chest expansion was limited on the left. No heart or breath sounds were heard over the left chest. The right cardiac border was percussed 2 cm. lateral to the right sternal border. Percussion note was hyperresonant in the left posterior chest and axilla, with diminished breath sounds in the left chest. The trachea was shifted to the right. Hemoglobin was 15 gm.; white blood cells were 22,000. Chest x-ray showed complete pneumothorax on the left, with a small amount of fluid in the left base. The heart was shifted to the right. An hour after admission the patient's condition became worse, with increasing dyspnea and cyanosis. Diagnostic aspirations of the left base revealed blood. A needle was placed at the fourth interspace and attached to an underwater tube in an attempt to relieve his symptoms, which were thought to be due to tension pneumothorax. There was associated improvement of his dyspnea and cyanosis.

On the patient's second hospital day, blood began to go into the trap bottle when he coughed. X-rays revealed increased fluid in the chest and, despite aspiration of 500 c.c. of blood, recheck films that evening showed progressive increase of fluid in the chest. His blood count dropped to 12.5 gm. Later that evening 700 c.c. more blood were removed and, in addition, several hundred cubic centimeters of blood had gone into the drainage bottle. Despite this blood loss, the patient showed no real shock, although his blood pressure dropped to 90/60 mm. of Hg and his pulse went up to 116. But on his third day, dyspnea and orthopnea were more marked and x-rays showed increasing fluid in the chest. A blood transfusion was given, but his hemoglobin remained at 12.5 gm. He was perspiring and cool, and was felt to be in borderline shock.

Plasma was started later in the day. Numerous laboratory tests showed no evidence of any blood dyscrasia. That evening the hemoglobin was 10 gm., and 1,500 c.c. of blood were removed from the chest. Shortly thereafter, because of this continued bleeding, he was taken to the operating room and an exploratory thoracotomy was done. The left lung was found to be completely collapsed, and a large amount of clotted blood and fibrin was found in the chest. Oozing was present in adhesions of the apex and of the left costophrenic angles. Although the oozing was considerable, no definite active bleeding points were seen. There were adhesions between the base of the lung and the parietal pleura. Repeated expansion of the lung failed to reveal any source of leakage. The bleeding was controlled by ligature of the adhesions and by the use of multiple gelfoam packs. An intercostal catheter which was attached to an underwater drainage system was introduced into the thoracic cavity through the ninth interspace at the anterior axillary line. The patient tolerated the procedure well. He was given 1,000 c.c. of blood during the operation. His postoperative course was smooth. Because of depression of the hemoglobin to 9.5 gm. on his first postoperative day, he was given another 500 c.c. of blood.

X-rays the first few days after thoracotomy showed absence of fluid and complete inflation of the left lung. X-rays the third postoperative day showed aeration to be almost as good on the left as on the right. An additional 500 c.c. of blood were given.

On the fourth postoperative day the patient was up and eating a full diet. He was discharged on the tenth day, and was able to return to work in two weeks. He has had no difficulty since this episode two years ago.

Case 4. A 21 year old girl was admitted to the hospital with acute respiratory distress which had started the day of admission. Pain began between the shoulder blades and extended around the left costal cage. There was no history of injury or tuberculosis. At the time of admission her pulse was 130, respiration 34, and blood

pressure 90/80 mm. of Hg. Mediastinal shift was evidenced by the trachea's being pushed to the right and by hyperresonance and absence of breath sounds in the left chest. X-rays revealed 500 to 1,000 c.c. of fluid in the left thoracic cage in addition to pneumothorax. The initial hemoglobin was 10 gm., with 3,900,000 red blood cells. In spite of aspiration of about 500 c.c. of blood on the evening of admission, chest films later showed large amounts of fluid. The next day the patient was transfused. The blood pressure remained about 110/60 mm. of Hg, with a pulse of about 90 to 100. Because there was evidence of continued bleeding with possible clot formation, as interpreted by the roentgenologist, thoracotomy was done about 40 hours after admission. At that time about 1 pint of coagulated blood and the same amount of bright red blood were found in the left thorax. At the extreme apex, a bleeding point was found in adhesions attached to the parietal pleura. The remaining portion of the lung appeared to be normal after inflation. The bleeding point was treated with a small piece of oxidized gauze after the adhesions were freed, and an area of bleb formation in the apex of the left lung was excised. The blood clot was removed manually and the chest was closed without drainage. The patient's postoperative course was uneventful and she was discharged 10 days postoperatively. It was necessary to do two additional thoracenteses in the postoperative period to remove sanguineous pleural fluid. The patient has been in good health from her discharge up to the time of this writing, 18 months later. Chest films demonstrated good resolution.

Case 5. A 33 year old man had a sudden episode of chest pain the evening before admission and was treated conservatively at home, since his blood pressure was found to be normal. The next morning he was in shock, with a systolic pressure of 60/70 mm. of Hg. He was admitted to another hospital, at which time he had several convulsions. He complained of dyspnea and continued chest pain. Physical examination and x-ray led to a diagnosis of spontaneous hemopneumothorax. He was transferred to this hospital and on admission was dyspneic and uncomfortable in spite of oxygen therapy. There was limited expansion of the right chest, with absent breath sounds and hyperresonance on percussion above the fifth and sixth interspaces and with dullness below it. The heart seemed slightly shifted to the left, with the point of maximal impulse in the anterior axillary line. Blood pressure was 70/48 mm. of Hg, pulse was 96 and respiration was 34.

An hour after admission, 1,900 c.c. of blood and some air were aspirated from the right thoracic cavity at the midaxillary line. Following this, the patient's dyspnea was somewhat better; his blood pressure rose to 100/58 mm. of Hg and his pulse dropped to 92. Two hours after admission he had received 1,000 c.c. of blood, and his pressure had risen to 112/64 mm. of Hg, with a pulse between 80 and 90. He was immediately transferred to the operating room for an exploratory thoracotomy. About 500 c.c. of clotted blood were found in the right thoracic cavity, in addition to a moderate amount of fresh blood. A small bleb was located in the apex of the right upper lobe which leaked when positive intratracheal pressure was used. The bleeding occurred from a small venous branch (which apparently originated from the subclavian vein near the apex of the thorax).

At the time of operation the bleeding points at the apex were ligated and the bleb formation in the right upper lobe was excised. A catheter was brought out through the anterior lateral aspect of the chest for underwater drainage. On the next day the patient appeared to be comfortable. An x-ray taken on the second day following the operation revealed 30 to 40 per cent aeration of the right lung.

On the third postoperative day, 750 c.c. of sanguineous fluid were removed, with a moderate amount of air. It was thought that there might be a continued leak with some bleeding, but the next day the lung was found to be 70 per cent inflated. Some fluid remained in the base.

On the tenth postoperative day, 600 c.c. of brownish fluid were aspirated, as well as 600 c.c. of air. There was continued clinical improvement, and the patient was discharged on the twelfth postoperative day. The subsequent course has been excellent, with no evidence of recurrence the past year. Chest films taken on discharge revealed complete expansion, with no residual pleural thickening or fluid.

Case 6. A 30 year old man developed a sharp pain in the scapula while in bed on the morning of admission. When moderate dyspnea developed he sought medical advice. He was sent home, but on his return to bed the pain became worse and the dyspnea had exacerbated. He was therefore hospitalized. On admission his blood pressure, pulse and respiratory rate were normal, but he had signs of mediastinal shift, with the trachea and heart both shifted to the right. A needle was inserted into the chest and attached to an underwater drain to relieve the tension pneumothorax. By the next morning a chest x-ray showed a collapsed lung on the left, with a fluid level about halfway up the chest. Blood had been seen coming through the needle inserted in the chest. After the x-ray, 600 c.c. of blood and 200 c.c. of air were removed from the left pleural space. Following this, an x-ray indicated that the lung expanded to about 60 per cent of its original volume and over two-thirds of the fluid had been removed. The patient's hemoglobin remained at 12.5 gm. during his hospitalization. He improved progressively without operation, and was discharged a week after admission with signs of almost complete resolution.

Case 7. This case is somewhat different in that the patient had a proved tuberculosis in the right upper lobe and, in April, 1949, was given a right therapeutic pneumothorax. As far as can be determined by records from previous institutions, the patient had no evidence of tuberculosis on the left. In November of 1950, while at home, he developed a very severe pain in the left lower chest which spread upward until it covered the entire chest. He found it difficult to catch his breath. He was hospitalized, and x-rays at the time disclosed bilateral pneumothorax, with fluid in the left chest. Two thousand cubic centimeters of blood were removed, and he was transferred to this hospital the next day.

On admission, the patient was found to be in moderate distress. There was dullness to percussion over the left lower lobe posteriorly, and hyperresonance over the left lower anterior lateral chest. There were decreased breath sounds in the left lower lobe posteriorly. The heart sounds were of good quality, with no audible murmurs. There were no signs of tracheal shift. Initial hemoglobin was 9.5 gm., with 2,500,000 red blood cells. X-rays confirmed the signs of hemopneumothorax. Five hundred cubic centimeters of blood were administered. Blood pressure, pulse and respiratory rate remained fairly constant during the night (blood pressure, 120/79 mm. of Hg; pulse, 120; respiration, 24). The next day, 1,250 c.c. of blood were removed from the left chest, penicillin was instilled in the pleural space, and 500 c.c. of blood were again given by transfusion.

The first and second days following admission there was continued clinical improvement. X-rays showed some pulmonary expansion and decrease of fluid in the left chest. It was felt both clinically and roentgenologically that the man had stopped bleeding.

On his seventh hospital day, 1,000 c.c. of blood were again aspirated from the chest, and the patient was given another 500 c.c. by transfusion. In total, he had six transfusions and about 2,500 c.c. of blood removed from the chest. He was discharged improved after one week's hospitalization, to be followed by the tuberculosis sanatorium. At the time of discharge, five months ago, his red blood cells were 4,300,000, with 14 gm. hemoglobin, and his lung had almost completely expanded.

Discussion

Our treatment of hemopneumothorax patients can be seen to follow a pattern in which the experience of the first cases has influenced the handling of subsequent ones.

We managed the first case of massive hemopneumothorax with the previously recognized conservative measures. The patient had more frequent aspirations than Hartzell recommended, but probably not so many as Moore would desire. He had a protracted hospital stay, and eventually required a decortication to allow expansion of the underlying lung.

The next man eventually needed decortication, despite minimal bleeding. This emphasized the necessity for a more radical approach to treatment. Therefore, when the case of the 33 year old man with massive hemopneumothorax did not respond after three days of conservative aspiration and transfusions, an exploratory thoracotomy was decided upon. The procedure proved successful. As can be seen from the last two cases, thoracotomy is by no means always necessary. The clinician must decide, as in cases of massive upper gastrointestinal bleeding, whether (and when) surgery is indicated.

This series of cases, seen over a three and one-half year period in a relatively small hospital, indicates that spontaneous hemopneumothorax is common enough that any doctor may be called upon to treat it. As has been previously indicated, the prevailing conservative therapy, consisting of mere watchful waiting or frequent aspirations and replacement transfusions, is often not sufficient, especially in the presence of massive bleeding.

The seriousness of this condition is emphasized by Arst's [7] report of a 22 year old man who died following conservative therapy alone. Myers [12] concluded from his review of the literature that the mortality rate approached 25 per cent under prevailing methods of treatment. In March, 1951, he reported the first published case of hemopneumothorax treated by surgery. His case had a rapid, uncomplicated recovery. His experience, plus that of the present series, demonstrates that a rapid recovery is possible with surgery, in contrast to the usual prolonged hospitalization and illness necessary for the severe cases under conservative management. The report by Nalls and Matthews [9] confirms our experience that, although the end result may be satisfactory by the use of aspiration alone, some cases will end with an entrapped lung which will eventually need decortication, with its associated prolongation of the patient's illness. Our first patient was unable to return to work for three months. An early thoracotomy to control bleeding and to remove clotted blood has an obvious advantage. However, an immediate thoracotomy merely to obviate a subsequent decortication is probably not necessary, now that streptokinase and streptodornase are available. According to a personal communication from Tillet, these enzymes have been used with success in preventing clot formation in the chest.

SUMMARY

1. Experiences in the treatment of seven cases of hemopneumothorax on the Chest Service of the Memorial Hospital have been described.

2. The literature on this subject has been reviewed.

3. Four important recommendations in the treatment of hemopneumothorax are offered:

A. Prompt aspiration of both blood and air, to facilitate pulmonary re-expansion. (Frequent x-ray will be necessary to help determine the times for re-aspiration.)

B. Early thoracotomy in cases of uncontrollable bleeding.

C. Use of streptokinase and streptodornase after the acute bleeding is over, to remove the residual clots and fibrin.

D. Early pulmonary decortication when organizing hemothorax is interfering with pulmonary reëxpansion.

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NOCARDIOSIS: THREE CASE REPORTS *

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Introduction

Nocardiosis is an acute or chronic infectious disease of granulomatous or suppurative nature, caused by an aerobic, gram-positive, inconstantly acid-fast species of the family Actinomycetaceae. *Nocardia asteroides* is the organism most frequently isolated. The authors wish to add three cases to the 43 recorded in the literature.

Review of the Literature

In 1888 Nocard [1] isolated aerobic Actinomyces from bovine farcy, and two years later Eppinger [2] reported a case in which similar organisms were cultured from a brain abscess. Henrici and Gardner [3] were able to collect 26 cases from the literature in 1921. The review of Kirby and McNaught [4] summarized 32 recorded cases, with 28 fatalities. In 20 instances the diagnosis was established at necropsy. Pulmonary lesions occurred in 26 of the fatal cases, and postoperative peritonitis in two cases. Brain abscesses were encountered in at least 10 instances. Pulmonary lesions were apparently arrested in two of the survivors by surgical drainage and sulfonamide or iodide and x-ray therapy. One other patient underwent amputation for madura foot,† while another showed a temporary response to autogenous vaccine therapy with subsequent recurrence of symptoms; the final outcome is unknown. Two fatal cases were added by these authors, one with generalized systemic lesions, the second with a solitary brain abscess. Eckhardt et al.[5] reported a similar case of solitary brain abscess without extraneural involvement. In this case the portal of entry was presumed to be a tooth socket, a common route of infection by *Actinomyces bovis.* Shaw [6] and Hager [7] each successfully treated a case of empyema by surgical drainage, sulfadiazine, iodide and penicillin therapy. Hager's second case succumbed to extensive pulmonary involvement. Calero [8] described a girl with "pleuro-pulmonary fistulae" who was considered cured following treatment with sulfonamides and penicillin. Glover et al.[9] added a case simulating pulmonary tuberculosis, with an apparent complete recovery after intensive sulfadiazine therapy. In this patient, no response had

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† The inclusion of this case in this group is questioned because of the difference in clinical course and the wide variety of etiologic agents isolated.

been obtained with penicillin and streptomycin. Tucker and Hirsch [10] published three cases; one had draining subcutaneous sinuses and a brain abscess, the second exhibited a granuloma of the left nostril and pulmonary involvement, and the third revealed a firm mass under the right mandible. All cases were treated with sulfadiazine, penicillin and streptomycin. The first two terminated fatally. The third patient responded favorably following surgical drainage and supplemental therapy with potassium iodide. Cuttino et al.[11] isolated a previously undescribed organism (*Nocardia intracellularis*) from a 34 month old girl with generalized superficial lymphadenopathy. Autopsy revealed massive involvement of the retroperitoneal lymph nodes. Similar findings have not been described in infections by *Nocardia asteroides*.

Clinical

The clinical course is often dominated by signs and symptoms referable to the respiratory system, and frequently simulates pulmonary tuberculosis. Anorexia, malaise, weight loss, night sweats, fatigue, chills, fever and a chronic cough productive of foul green sputum are commonly recorded complaints. Hemoptysis occasionally occurs. In a few cases pulmonary symptoms have been lacking, and in these instances subcutaneous abscesses and sinuses or neurologic manifestations indicative of a brain abscess have been encountered. Hepatomegaly and splenomegaly, as well as alimentary and urinary tract abnormalities, have been described, but these represent the late stages of widely disseminated infections. Roentgenograms of the chest may simulate any of the changes produced by other more common infectious granulomata.

Pathogenesis

Key to Genera of the Order Actinomycetales *

Mycobacteriaceae (family)
- Mycobacterium (genus)

Actinomycetaceae
- Actinomyces—anaerobic
- Nocardia—aerobic
  - non-acid-fast
  - acid-fast

Streptomycetaceae
- Streptomyces
- Micromonospora

The Actinomycetaceae include organisms that are both mold- and bacteria-like. The organisms have extremely fine mycelium, varying from 1μ

* Adapted from Waksman and Henrici.[12]

to less than 2μ in diameter. There is a main or axial filament with true lateral branches.[13] Nocardias are aerobic organisms with a vegetative mycelium dividing by segmentation into bacillary or coccoid elements.

Cultural Characteristics

The Nocardias grow well on the usual culture media under aerobic conditions, and for the most part prefer an alkaline medium. Colonies appear within 36 to 72 hours, in a temperature range of from 20° to 37° C. Sometimes mycelial ball-like colonies assume a "star shaped" appearance, ergo the designation "asteroides." In liquid media, *N. asteroides* tends to form a dry, wrinkled pellicle floating on the surface. The aerobic Nocardias do not ferment carbohydrates and do not produce indole, hydrogen sulfide or ammonia.[14] Simple hydrocarbons such as paraffin can be utilized to support growth.

The usual sodium hydroxide (3 to 4 per cent) method (incubation for 30 minutes) for concentration of sputum for tubercle bacilli supposedly destroys Nocardia, and therefore culture or animal inoculations are negative.[7] However, in two of our cases growth occurred after such treatment. Cuttino et al.[11] reported similar behavior with *N. intracellularis.*

Tinctorial Properties

The Nocardias are gram-positive, and either partially or nonacid-fast. Represented in the acid-fast group are *N. asteroides, N. brasiliensis* and *N. intracellularis.* The acid-fast property tends to disappear with subculturing. If, instead of the usual Ziehl-Neelsen technic, a weak solution of sulfuric acid is used to decolorize, the acid-fast characteristic may be observed in spite of several transfers.[7] Different strains show varying degrees of acid-fastness.

In tissues and exudates, the Nocardias appear as granules of different colors, *N. asteroides* being generally yellow. Acid-fastness appears to be more pronounced in tissues and exudates than in cultural material.

Tissue Pathology

In the great majority of instances, the lungs are either primarily involved, or pulmonary metastasis from some other focus occurs early in the disease. In the lung a caseous bronchopneumonia with eventual softening and cavitation ensues, and there is a pronounced tendency for hematogenous dissemination with abscess formation in brain, liver, spleen, kidney, adrenals, intestinal wall, muscles, subcutaneous tissue and skin.[7] Pulmonary lesions frequently extend to the pleura, giving rise to empyema.[6, 7] In a number of cases old lesions are found which suggest that the disease may have been localized for as long as 15 years before becoming generalized.[15, 16]

Microscopic Pathology

The microscopic change in nocardiosis is characterized by a lesion whose center is composed of necrotic material and surrounded by an area of dense cellular fibrous tissue, fibrin, leukocytes, plasma cells and macrophages, with branching organisms scattered throughout the tissue.[4, 14] On occasion, "granules" appear in the tissues as amorphous lobulated masses (delicate tangled hyphae).

Virulence in Laboratory Animals

N. asteroides is inconstantly pathogenic for the guinea pig and rabbit. Intravenous or intraperitoneal inoculation usually produces miliary abscesses in the viscera or peritoneum, and some animals die within seven to 14 days. Subcutaneous or intramuscular injection produces only localized disease, with eventual rupture to the outside or spontaneous healing.[7]

Portal of Entry

Although *N. asteroides* has been isolated widely from the soil [13] the route of entry into the body is unknown.

Case Reports

Case 1. A 39 year old disoriented white male was admitted to Jewish Hospital on February 10, 1951. The patient had been partially disabled since 1939 by advanced silicosis following a two year occupational exposure in a tile factory. In November of 1950 he noted malaise, fever and night sweats. In December he developed a subcutaneous abscess involving the left thigh. Thereafter, subcutaneous lesions of a similar nature appeared in disseminated fashion. On admission he appeared acutely ill. Temperature, 99° (R); pulse, 132; respirations, 24; blood pressure, 118/60 mm. of Hg. Numerous fluctuant subcutaneous abscesses were distributed over the entire body. Some of these had broken down to form circumscribed ulcers with sharp margins and reddish gray bases. The lungs were clear. The heart and abdomen were not remarkable. Aside from a cloudy sensorial state, neurologic signs were absent. The red cell count was 3.0 million per cu. mm.; hemoglobin, 8.0 gm. per cent; white cell count, 15,900 per cu. mm., with 90 per cent neutrophils. Occasional pus cells were noted in the urine. Adequate sputum specimens were not available for acid-fast staining. Cultures of pus aspirated from the subcutaneous abscesses were positive for *N. asteroides* on two occasions. X-ray of the chest revealed patchy infiltrates in the upper portions of both lung fields and a questionable widening of the upper right mediastinal shadow. These findings were compatible with silicosis, and the possibility of superimposed tuberculosis was considered. In spite of intensive antibiotic therapy consisting of aureomycin, streptomycin, penicillin, promacetin and supportive measures, the patient continued on a downward course. Objective neurologic findings consisted of a progressive deterioration of the sensorium. The patient died on March 5, 1951.

Necropsy: Multiple subcutaneous abscesses involving the neck, chest, abdomen and lower extremities were seen. Several abscesses drained a creamy green exudate. Deep seated abscesses were encountered in the abdominal musculature. *Lungs:* The right lung weighed 1,200 gm. and the left 1,000 gm. Crepitation was diminished bilaterally. Gray nodules (1 to 2 mm.) were present in the pleura. Sectioning

revealed two completely different lesions in both lungs. The central portion was occupied by a firm, black, compact, airless mass (anthracosilicosis). The peripheral region showed multiple cavitations, the largest being 4 cm. in diameter (right apex). The cavities contained cream colored pus. Aerated parenchyma peppered with 1 to 2 mm. grayish nodules was seen between the two types of lesions described above. The smaller pulmonary arteries showed occlusion by emboli (arising from an ad-

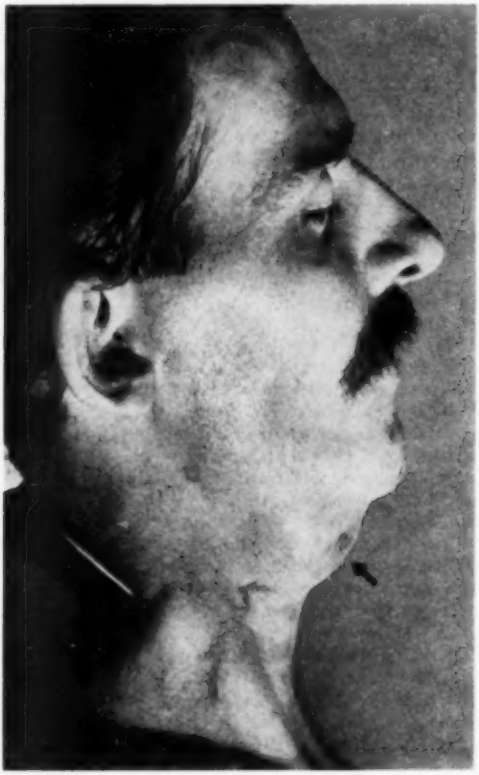

FIG. 1. *Case 1.* Postmortem photograph demonstrating a large subcutaneous abscess just beneath the chin.

herent thrombus in the inferior vena cava). A 4 mm. mucosal ulceration was found in the trachea 2 cm. above the carina. The hilar nodes were enlarged and firm, and sectioning displayed anthracotic deposits throughout. *Kidneys* together weighed 600 gm. The cortex was smooth. Cross-section divulged several cortical abscesses (2 to 4 mm. in diameter) similar to those already described. The *brain* weighed 1,630 gm. The leptomeninges were covered diffusely by a yellowish green exudate. Coronal sections disclosed multiple yellowish green nodules (1 to 2 cm. in diameter)

in the gray matter of the cerebrum and cerebellum. The remaining viscera were not remarkable.

Microscopic: Lungs: Two different but frequently combined processes were found: (1) foci exhibiting fibrosis, hyalinization, focal calcification and anthracosis, and (2) foci in which the alveoli were filled with neutrophils which were centrally located and were surrounded by fibrin and elongated histiocytes (epithelioid cells). Occasional mycelia were seen within vessels. The trachea showed a mucosal ulceration, with "collar button" submucosal extension and destruction of the underlying cartilage. The bronchomediastinal nodes showed extensive hyalinization, with some silicotic nodules and anthracotic deposits. No acute inflammation was seen in any of the lymph nodes. The *subcutaneous tissue, muscle, kidneys* and *brain* showed the

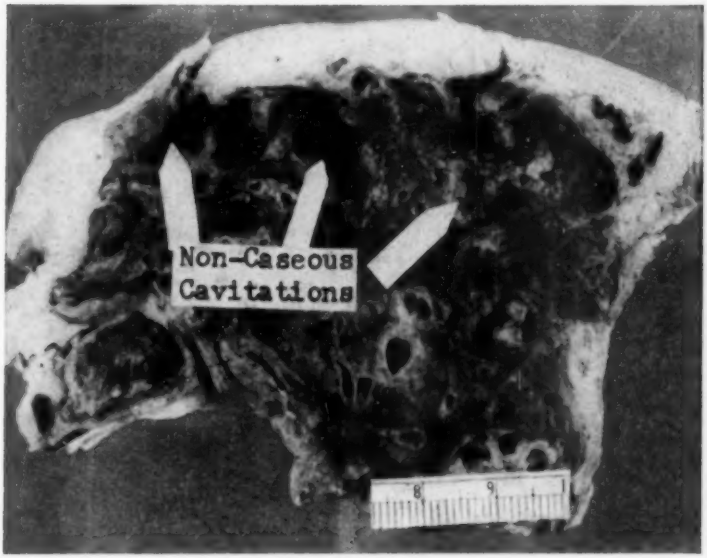

FIG. 2. *Case 1.* Gross section of right lung, revealing numerous peripheral noncaseous cavitations.

typical lesion of nocardiosis, characterized by central suppuration and peripheral collection of histiocytes. Hyphae with occasional branching were demonstrated in the brain, lungs and kidneys; these did not take the acid-fast stain. No granules or giant cells were demonstrated.

Cultural Studies: Aspiration of pus from three different areas revealed in each instance branching hyphae which were thin and appeared as simple threads. After 48 hours white, dry, chalky colonies appeared on blood agar plates incubated at 37° C. After three to six weeks they did not increase above a diameter of 4 to 5 mm. On plain agar and Sabouraud's glucose agar, similar colonies developed which after three weeks exhibited a characteristic pigmentation best seen through the back of the culture—a deep orange center surrounded by a pale yellow zone. Gelatin was not liquefied until after six weeks. In the incubator the growth on gelatin occurred in

the form of flat, white, nonconfluent surface colonies. Litmus milk turned alkaline after a few days. When stained by the Kinyoun method, the organism proved to be acid-fast. The branching tendency was seen constantly in culture mounts and in stained preparations. The organism was not sensitive to aureomycin, terramycin, chloromycetin, bacitracin or sulfadiazine, but was slightly inhibited by a combination of penicillin (22 units/c.c.) and streptomycin (40 units/c.c.). Diagnosis: *N. asteroides.*

Case 2. A 60 year old white male entered the Cincinnati General Hospital March 19, 1951, and died four days later. He had been employed at odd jobs and had been well until November, 1950, at which time he developed a persistent cough productive of thick yellow-green sputum. Two weeks prior to admission he had noted

FIG. 3. *Case 1.* Left lung, showing central area of anthracosilicosis and many 1 to 2 mm. nodules surrounding this zone.

the onset of shortness of breath, ankle edema and a left axillary mass. The latter was incised and drained in the Out Patient Department three days prior to his admission. On admission the patient appeared acutely ill, semistuporous and dyspneic. Temperature, 103.2° F.; pulse, 120; respirations, 36; blood pressure, 160/80 mm. of Hg. The neck resisted anteflexion. A "furuncle" with a crusted surface was noted in the left axilla. The percussion note was dull over the right chest, and fine moist râles were heard over both lung fields. Systolic murmurs were audible in the aortic area and at the apex. There was marked pitting edema of the lower extremities. Deep tendon reflexes were slightly more active on the left, and the plantar response on this side was equivocally reversed. Red cell count, 4.88 per cu. mm.; hemoglobin, 12 gm. per cent; white cell count, 28,200 per cu. mm., with 78 per cent neutrophils. The urine gave a 2 plus test for albumin. Serologic tests for syphilis on blood and

spinal fluid were negative. Type XXIX pneumococci and *Staphylococcus aureus* were cultured from the sputum, but concentration studies for acid-fast organisms were negative. A lumbar puncture, performed with good relaxation, revealed an initial pressure of 220 mm. H_2O and a final pressure of 180 mm. H_2O after removal of 15 c.c. of ground glass fluid. The fluid contained 910 leukocytes per cubic millimeter, of which 60 per cent were neutrophils. Spinal fluid glucose was 43 mg. per cent and the total protein was 66 mg. per cent. Thoracentesis recovered 420 c.c. of bloody fluid from the right chest. Routine cultures of the pleural fluid, cerebrospinal fluid and blood were negative, but "diphtheroids" were isolated from the left axillary mass. An x-ray of the chest disclosed fluid in the lower two-thirds of the right thorax. An area of increased density was thought to be present in the right lower lung field.

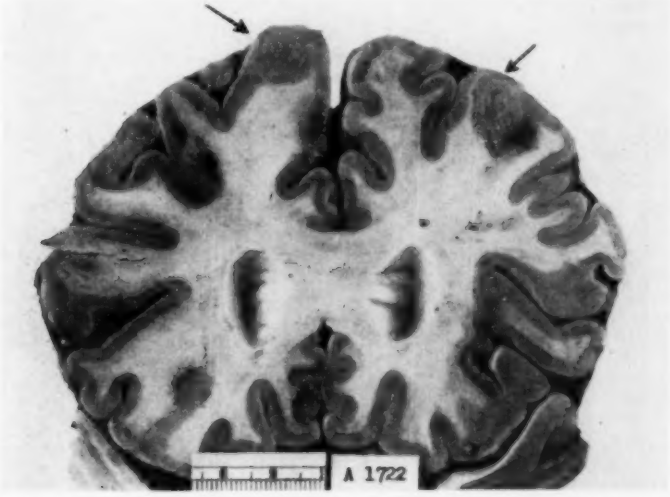

FIG. 4. *Case 1.* Coronal section of cerebral hemispheres with scattered abscesses in both gray and white matter.

The patient was treated for cardiac failure with digitalis and mercurial diuretics. The possibility of a brain abscess secondary to a right-sided pneumonia with pleural effusion was strongly considered, and the patient received intensive sulfonamide, penicillin, streptomycin and aureomycin therapy, but they failed to alter his progressively downward course.

Necropsy: A skin defect was present in the left axilla overlying a small subcutaneous mass, but no drainage was observed. The right pleural cavity contained 500 c.c. of serosanguineous fluid which was partially loculated by stringy fibrinous adhesions. The right *lung* weighed 700 gm. and the left 450 gm. The right middle and lower lobes were atelectatic and streaked with gray fibrous tissue. The remaining lobes were moderately congested. The bronchi were prominent and contained a yellowish green exudate. The *brain* weighed 1,185 gm. and was externally not remarkable. Coronal sections through the cerebral hemispheres disclosed a 2.0 cm. abscess in the left occipital lobe communicating with the posterior tip of the left lateral

ventricle. The abscess was lined by a thin wall of granulation tissue and contained yellowish green pus. A similar exudate coated the lining of the left lateral ventricle. Cultures of the pleural fluid, left lateral ventricle and occipital abscess were positive for *N. asteroides*.

Microscopic examination of the *brain* revealed an acute suppurative ventriculitis. The occipital abscess contained degenerating neutrophils. In the surrounding brain

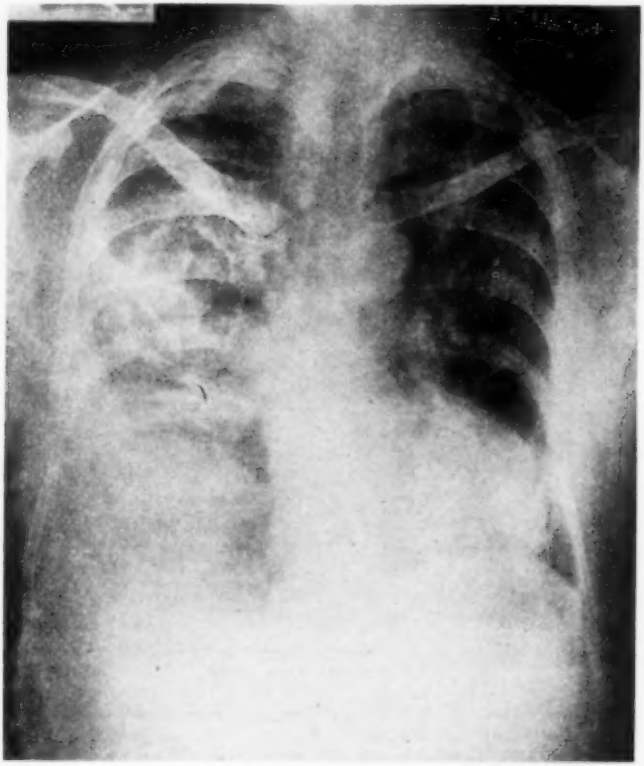

FIG. 5. *Case 2.* Posterior-anterior chest x-ray. Multiple encapsulations of pleural fluid in the right hemithorax; cardiac displacement by fluid and/or the clinically apparent pectus excavatum.

tissue there was a mild pleomorphic perivascular reaction, occasionally accompanied by small vessel thrombosis. Sections stained by the Glynn gram- and acid-fast [18] technics demonstrated granular, branching, filamentous, gram-positive, weakly acid-fast organisms. The right middle lobe of the *lung* was the seat of a chronic inflammatory reaction associated with parenchymal atelectasis and fibrosis. A small subpleural abscess contained necrotic neutrophils, and its wall was infiltrated by lymphocytes, histiocytes and occasional multinucleated giant cells. The overlying pleura

showed an acute and focally organizing fibrinous pleuritis. The *subcutaneous tissue* in the left axilla was the seat of a chronic inflammatory reaction characterized by a lymphocytic and histiocytic infiltrate as well as an occasional giant cell.

Cultural Studies: After 48 hours white, dry, chalky colonies appeared on blood agar and Sabouraud's glucose agar incubated at 37° C. The organism stained with Kinyoun was acid-fast. A branching tendency was constantly observed. Litmus milk became alkaline after 60 days. Gelatin was not liquefied.

Case 3. A 23 year old white female entered Jewish Hospital November 9, 1947, complaining of shortness of breath, orthopnea, night sweats and hemoptysis of four days' duration. Physical examination revealed a well developed, well nourished patient, in the fourth month of pregnancy. Dullness, decreased tactile fremitus and diminished breath sounds were observed over the left hemithorax, with scattered râles audible at the right base. There were cyanosis and clubbing of the digits of both hands. Laboratory studies revealed a red cell count of 4.5 million per cu. mm.; hemoglobin, 8.2 gm. per cent; white cell count, 15,000 per cu. mm., with 88 per cent neutrophils. Urinalysis revealed a few pus cells and 30 mg. per cent albumin. A posterior-anterior roentgenogram of the chest demonstrated massive pleural effusion of the left hemithorax displacing the heart and mediastinum to the right. The right pleural field was negative. Thoracentesis yielded serosanguineous fluid containing 1,000 erythrocytes per cu. mm., and 50 lymphocytes per cu. mm. The total protein of the fluid was 2,600 mg. per cent. Kinyoun stains of the pleural fluid demonstrated several acid-fast bacilli morphologically, similar to *Mycobacterium tuberculosis*. Repeated animal inoculations were negative. Cultures inoculated with pleural fluid on December 1 were first observed on December 13. Present were confluent colonies which were moist and yellowish and which appeared only on the bottom of the tube. The organisms were slender Gram labile rods which were acid-fast and contained two to three granules in the body of the rod. The acid-fast part was often in the sharp end of the rods, which were usually straight in shape. Subcultures grew on Petragnani, blood agar, Dubois and thioglycollate media at room temperature and at 37° C. The rods were identified as a species of Nocardia.

The pregnancy was interrupted and the patient was treated with streptomycin and penicillin. The chest fluid persisted and the patient was transferred to a chronic disease hospital, where she was maintained on streptomycin and supportive penicillin therapy until discharge in July, 1948. The chest film at that time revealed a persistent left pleural effusion. In June and November, 1950, chest films showed pleural thickening on the left, with some persistent shift of the mediastinum. No pleural effusion was present, however. The patient is now asymptomatic and has withstood another pregnancy in the last year without recurrence of symptoms.

Comment

Although the diagnosis was established before death in case 1, the patient represented such a terminal stage of the disease that the therapeutic approach, albeit intensive, was ineffectual. It is noteworthy that this man had preëxisting pulmonary silicosis, a circumstance not encountered in the literature. Whether silicosis proved a fertile medium for nocardiosis, as is commonly the case in pulmonary tuberculosis, can only be a matter of conjecture in this instance.

Case 2 is illustrative of the frequent combination of pulmonary and neurologic manifestations. In contrast to case 1, antemortem studies failed to reveal the etiologic agent. We can offer no satisfactory explanation for

this, inasmuch as postmortem cultures yielded *N. asteroides*. "Diphtheroids" isolated from the left axillary mass may have represented broken filaments of *N. asteroides*.

The third case is classified as a "cure," and has evidenced no recurrence during four years of follow-up. The similarity of the signs and symptoms to those of pulmonary tuberculosis was striking. Also impressive was the favorable response to combined penicillin-streptomycin therapy, a result not observed in the literature heretofore.

Since nocardiosis may mimic pulmonary tuberculosis, it is important that one appreciate the fact that fragmented acid-fast mycelia in sputum may be mistaken for *Mycobacterium tuberculosis*.

Treatment

The antibiotic and chemotherapeutic agents that are effective in inhibiting *N. asteroides* in vitro should be utilized either alone or in combination. Of the sulfonamides, sulfadiazine and sulfamerazine seem to be the most active and least likely to cause toxicity.[4, 7, 9, 10, 19, 20] In some cases, when a sufficiently high blood level has been obtained, penicillin has been found to inhibit the organism.[20] In vitro streptomycin in high concentration inhibits the organisms, but equivalent dosages utilized clinically may result in eighth nerve damage.[21] There is as yet insufficient evidence regarding the effectiveness of aureomycin, terramycin and chloromycetin. In the cases reported to date, the organisms have been found more sensitive to sulfadiazine than to the antibiotics. Therefore, at this time sulfadiazine should be incorporated in the treatment of nocardiosis with indicated adjuvants.

Summary

1. Nocardiosis is an infectious disease due to an aerobic, gram-positive, inconstantly acid-fast species of the family Actinomycetaceae.

2. The literature is reviewed and three new cases are added to the 43 previously reported.

3. Clinical course, bacteriologic and pathologic findings are reported in detail.

4. The effectiveness of chemotherapeutic and antibiotic agents is evaluated. Sulfadiazine should be included in combined therapy and other drugs evaluated by sensitivity tests. Surgical drainage should be employed when indicated.

5. In our cases there were two fatalities; one patient is at present asymptomatic after a four-year follow-up. One of the fatal cases was associated with preëxisting anthracosilicosis.

Acknowledgment

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CARDIAC ASTHMA: ITS PATHOGENESIS AND RESPONSE TO AMINOPHYLLINE*

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THE voluminous reports bearing upon the pathogenesis of cardiac asthma, its relationship to bronchial asthma and the value of aminophylline in therapy present basic disagreements regarding both the statistical evaluation and the theoretic concepts. In an effort to clarify some aspects of these rather controversial subjects, a group of cases was collected for study. We were particularly concerned with the circulation times and the clinical response to intravenous aminophylline therapy as a suitable means of approach. The statistical summations are complemented by theoretic consideration when necessary.

The cases were selected from approximately 2,000 bronchial asthma and cardiac admissions to the adult wards of a general hospital service during a three year period.† The findings of dyspnea and associated wheezes comprised the first requisites. Moreover, only those cases were included in which the symptoms occurred as an acute episode. Similar attacks may have taken place previously, but there were no intervening related symptoms prior to the present attack. The admission diagnosis of cardiac or bronchial asthma was based upon the character of the attack, the relevant family history, the presence of allergic manifestations, the cardiac status and the response to adrenalin and morphine. In some cases both diagnoses were admissible. Circulation times and the effect of intravenous aminophylline were used to help corroborate or negate a diagnosis, but in no case were they used as the criteria. The circulation time was performed as soon as possible following admission and prior to the administration of active therapy.

Circulation time determinations consisted of a single intravenous needle insertion. Decholin was administered in 3 c.c. quantity for arm-to-tongue time, and the reaction was noted at the first appearance of bitter taste. The arm-to-lung time was then determined by injection through the same needle of 2 c.c. of equal quantities of physiologic saline solution and ether. The detection of ether odor in the patient's breath determined the end point. It was impossible to perform these tests on some patients because of their critical condition, but in a few such instances the ether test was possible by virtue of its objective character.

* Received for publication July 13, 1951.
† From the Medical Services of Gouverneur Hospital, New York.

Analysis of Table I

The number of cases studied was 75. Bronchial asthma was diagnosed in 30 (40 per cent), and cardiac asthma in 35 (46.7 per cent); the remaining 10 (13.3 per cent) were considered to have both cardiac and bronchial asthma. Many of these patients had learned of their diagnosis previously, since the majority were victims of repeated attacks.

In the 30 bronchial asthma cases, there were 26 arm-to-lung determinations and 25 arm-to-tongue. Practically all results fell within normal limits.* In only two cases was the arm-to-lung time found to be as long as 10 seconds, and in one of these the arm-to-lung time was found to be five seconds on a repeat determination. The pulmonary circulation time of this case was six seconds, placing it in the lower limits of normal.† Arm-to-tongue time was found to be within normal limits in uncomplicated bronchial asthma by Cottrell and Cuddie [1] and others, whereas an increase in the circulation time has been found in left ventricular failure or congestive heart failure.[2, 3, 4]

Thirty-five (46.7 per cent) were admitted as cardiac patients. Four of these were too critically ill to permit both determinations. Only the arm-to-lung time was possible in these, and in all four it was above 20 seconds. No determinations were done in two cases in extremis. The arm-to-tongue time was found to be above normal in the 29 determinations. There was only slight variation in the circulation times on repeated determinations in several cases. In the cardiac group the time remained above normal for each of two readings taken at different periods. This is consistent with the permanent increase in circulation time of chronic cardiacs as found by Hitzig, King and Fishberg.[3]

In all, 10 cases (13.3 per cent) were diagnosed as having cardiac failure and bronchial asthma. The circulation times (arm-to-lung and arm-to-tongue) were determined in nine of the 10. The arm-to-lung time ranged from six to 17 seconds and from 10 to 42 seconds in the arm-to-tongue time. On the basis of circulation time, five of these cases were considered to belong to the asthmatic group, while four were classed as cardiacs. In the former the A-L time of the five ranged between six and nine seconds, while the A-T range was between 10 and 15 seconds. The cardiac group had an A-L time of 17 seconds for three cases and 13 for one case. The A-T time was 29 seconds or above for all four.

Aminophylline

The administration of intravenous aminophylline (7.5 grains in 20 c.c. of saline) immediately followed the circulation time determinations. It

* Normal circulation times. Arm-to-lung (A-L) for ether, 3.5–8 sec. Arm-to-tongue (A-T), 8–14 sec. for Decholin. (Cecil, R. L., and Loeb, R. F., editors: Textbook of Medicine, 7th Ed., 1947. W. B. Saunders, Philadelphia.)

† Pulmonary circulation time (A-T time minus A-L time) is 5–17 sec. (Best, C. H., and Taylor, N. B.: Physiological Basis of Medical Practice, 2nd Ed., 1939, Williams and Wilkins Co., Baltimore.)

TABLE I

	Name	Age	Diagnosis	Circulation Time (in seconds)		Effect of Aminophylline	
				Arm to Lung	Arm to Tongue	Wheezes	Dyspnea
1	A. B.	27	Asthma	7	13	xx	xx
2	M. B.	63	Asthma	8	14	?	x
						xx	xx
				5	12	x	xx
3	A. S.	65	Asthma	10	16	?	x
				5	7	x	xx
4	S. L.	52	Asthma	2	13	?	xx
5	L. S.	20	Asthma			xx	xx
6	L. K.	43	Asthma	6	14	x	x
7	A. T.	36	Asthma			0	x
							x
				7	12	0	x
8	D. S.	34	Asthma	8	14	?	xx
9	L. W.	64	Asthma	7	13	?	xx
10	S. M.	55	Asthma	5	7	?	xx
11	E. C.	45	Asthma	10	14	xx	xx
				?		0	0 D.
12	L. M.	19	Asthma			?	xx
13	A. S.	37	Asthma	6	12	0	xx
14	R. H.	52	Asthma				
			URI	7	16	0	x
15	R. S.	21	Asthma			?	xx
16	W. S.	49	Asthma			?	xxx
						?	xxx
						?	xxx
17	A. R.	25	Asthma			?	xx
18	J. L.	54	Asthma	9	16	?	xxx
19	M. K.	49	Asthma	7	?	?	x D.
			RLL PN				
20	R. G.	57	Asthma	8	14	x	xxx
21	I. B.	60	Asthma	5	13	?	xx
22	I. B.	41	Asthma	7	15	?	xxx
			URI				
23	A. L.	68	Asthma	5	12	0	xx
24	R. R.	40	Asthma	4	11	x	xxx
25	R. A.	53	Asthma	8	13	?	xx
26	W. G.	65	Asthma	7	12	?	xx
			Bronchitis				
27	A. C.	52	Asthma	6	14	xx	xx
28	E. B.	60	Asthma	8	17	xx	xx
29	J. F.	70	Asthma	8	15	?	xx
							xx
						?	xxx
30	J. L.	54	Asthma	8	17	?	xx
			Bronchiectasis			xx	xx
						xx	xx
						xx	xx
31	J. G.	43	RHD				
			Essential hypertension	12	27	0	0 D.
32	H. C.	73	HCVD	12	29	0	0
33	M. S.	80	HCVD	17	23	0	0
34	J. M.	38	HCVD	15	27	0	0
35	N. H.	67	ASHD	?		0	0 D.
			Cerebral accident				
36	J. C.	60	Chronic cor pulmonale	22	47	0	0
			Emphysema	17	30	0	0
			ASHD	?		0	0 D.

TABLE I—*Continued*

	Name	Age	Diagnosis	Circulation Time (in seconds)		Effect of Aminophylline	
				Arm to Lung	Arm to Tongue	Wheezes	Dyspnea
37	P. S.	45	Chronic cor pul. ASHD	40 20 20	? 40 35	0 0	0 0 D.
38	W. F.	77	HCVD Uremia	30	?	0	0 D.
39	P. S.	74	ASHD	?	?	0	0 D.
40	E. F.	53	Chronic bronchitis RHD (inactive)	12	15	x	xx
41	G. F.	82	HCVD	13	30	0	0 D.
42	R. S.	55	HCVD	25	30	0	0
43	A. G.	70	ASHD	13	29	0	0 D.
44	S. G.	74	Chronic bronchitis HCVD	9	16	xx	xxx
45	A. K.	65	HCVD Bronchiectasis	9	27	0	x
46	C. K.	67	HCVD Bronchopneumonia	5	73	0	0 D.
47	C. C.	66	HCVD Anemia	7	21	0	0
48	T. S.	64	HCVD	24	56	0	0 D.
49	J. B.	59	ASHD EH Bronchopneumonia	10 10	22 20	0 0	0 0
50	I. B.	51	HCVD	19	58	0	0
51	T. M.	72	ASHD HCVD	25	55	xx	xxx
52	L. M.	63	HCVD	40	25	0	0 D.
53	T. F.	54	HCVD	28	?	0	0 D.
54	J. M.	65	HCVD EH	17	43	0	0 D.
55	M. R.	68	ASHD	21	?	0	0 D.
56	S. B.	83	HCVD ASHD	16	29	0	0
57	B. S.	65	HCVD Bronchopneumonia	28	?	0	0
58	M. F.	58	ASHD TB	17	39	0	0
59	S. N.	88	ASHD Bronchopneumonia	8	17	0	0
60	H. G.	65	HCVD	21	22	0	0
61	C. C.	66	HCVD	7	21	0	0
62	J. G.	63	ASHD	18	33	0	0
63	I. F.	55	ASHD	18	32	0	0
64	L. Y.	50	ASHD	7	25	xxx	?
65	J. V.	66	ASHD	10	22	xx	xxx
66	R. W.	55	Asthma ASHD	8	10	xx	xx
67	B. C.	48	Asthma HCVD	6	13	0	xx
68	M. S.	79	HCVD Asthma	9	12	xx	xxx
69	E. R.	75	ASHD HCVD Asthma	7	15	x	xxx
70	W. C.	72	ASHD EH Asthma	9	14	?	xxx

TABLE I—*Continued*

	Name	Age	Diagnosis	Circulation Time (in seconds)		Effect of Aminophylline	
				Arm to Lung	Arm to Tongue	Wheezes	Dyspnea
71	M. G.	76	HCVD Asthma	17	32	0	0
72	M. K.	63	HCVD Asthma	13 10	27 15	0 ?	0 xx
73	G. W.	75	HCVD Asthma	17	42	0	0
74	P. P.	55	Asthma ASHD Bronchopneumonia	17	32	0	0
75	M. S.	68	Asthma ASHD	?		?	x

Total

Bronchial Asthma	30
Cardiac Asthma	35
Bronchial and Cardiac Asthma	10

Abbreviations

ASHD	Arteriosclerotic heart disease
EH	Essential hypertension
RHD	Rheumatic heart disease
HCVD	Hypertensive cardiovascular disease
URI	Upper respiratory infection
Pn	Pneumonia
D	Deceased
Effect of Aminophylline	Minimum 0 to maximum xxxx

was given very slowly over a 20 minute period. In addition to evaluating the clinical response, auscultatory changes were noted. Of the 30 diagnosed cases of bronchial asthma, dyspnea was improved in every case, although only moderately in four. Wheezes were altered in 11. The cardiac group was generally unimproved by aminophylline. Only four of these patients showed definite relief from dyspnea, and slight improvement was noted in one other case. As a further commentary on this group of four, two were revealed as asthmatics of long standing. The response of the mixed group is significant. The five cases classed as asthmatics on the basis of circulation times responded very well to aminophylline. All four grouped as cardiacs failed to evince any response to aminophylline. One of the mixed cases is noteworthy. It is listed as belonging to the cardiac group, the circulation times being A–L 13 seconds and A–T 29 seconds. There was no response to aminophylline. In a previous admission, the circulation times were A–L 10 seconds and A–T 15 seconds, and a response was obtained by aminophylline at that time.

NECROPSY

Four of the 16 deceased cases were examined at autopsy. All four were diagnosed as cardiacs on admission. Three were found to have advanced

atherosclerosis. The fourth was a case of hypertensive cardiovascular disease with chronic passive congestion. Three of the cases were in the hospital for a period of at least three weeks and one for five days. None had shown any response to aminophylline. One case had had a previous admission in which there was no response to aminophylline.

Discussion

The modern conception of cardiac asthma stems from Osler's classic description: "In cases of arteriosclerosis there are often attacks of dyspnoea of great intensity recurring in spasms, often nocturnal. The patient goes to bed feeling quite well, and in the early morning hours wakes in an attack which in its abruptness of onset and general features, resembles asthma. There is usually a sensation of precordial distress, a feeling of constriction and oppression, what the Germans call 'Beklemmung.' Two other features about this attack will attract your attention—the evident effort in the breathing and the presence of a wheezing in the bronchial tubes and the moist râles at the bases of the lungs. The patient will spring from bed and throw open the windows in his terrible air hunger, and he assumes an attitude most favorable to the working of all the accessory muscles of respiration. Slight cyanosis is usually present and in severe paroxysms a cold sweat breaks out in the face and limbs. The pulse is feeble, often irregular and very small, and on auscultation one hears either gallop rhythm or the foetal type of heart beat. Death may occur in the attack." [5]

The term cardiac asthma applies to a pulmonary condition which simulates bronchial asthma but which is associated or induced by cardiac failure. The onset is frequently nocturnal, the victim being aroused from sleep in the throes of an attack of shortness of breath and perhaps audible wheezes. The difficulty in breathing is somewhat alleviated by assuming the sitting position, which the patient continues to favor during the attack.

Cardiac asthma is frequently associated with left heart failure. Weiss and Robb [6] found the lungs in cardiac asthma to be engorged, and confirmed the presence of an excess quantity of blood in the lungs at autopsy. Sodeman [7] states that cardiac asthma is a manifestation of left ventricular failure, and may be called paroxysmal nocturnal dyspnea. The relationship between the two conditions has also been attested by Eppinger,[8] Traube [9] and others.

It is not entirely clear why a small percentage of cases of cardiac failure manifests the type of symptom complex called cardiac asthma. The mode of onset is an explosive seizure, usually initiated nocturnally and most often following a period of repose. Two factors combine to characterize the attack. In the first place, the suddenness of onset must result from an intrinsic mechanism defect. This is in contrast to the usual ventricular failure that follows undue strain of the heart incident to effort or excitement. The high incidence of coronary disease (38 per cent by electrocardiogram) found by Weiss and Robb [6] suggests the basic cause for cardiac asthma.

These investigators also found bundle branch block in 17 per cent of their cases. Harrison, Calhoun and Harrison [10] point out the frequent occurrence of premature beats and gallop rhythm in these cases. The relationship to coronary artery disease may also be inferred from the mortality statistics of Weiss and Robb,[6] who found that 44 of 87 patients died within one year. The rôle of coronary artery disease as either an insufficiency or occlusion may be suspected when one recalls Osler's description of the cold sweat, cyanosis, the feeble small irregular pulse, the gallop rhythm or fetal heart. Christie and Meakins [11] feel that cardiac asthma depends upon the suddenness of onset. Von Leube [12] held that under conditions in which the left ventricle rapidly weakened there is a sudden increase in pressure of the pulmonary capillaries. Browning [13] and others have documented the literature regarding the rapid mechanism involved in cardiac asthma.

The second factor depends on the fact that the attack occurs while the patient is lying down. In this position, unlike standing, there is no possibility of escape of blood to the extremities or to the abdominal vessels. Thus, the "cushioning" effect of these safety reservoirs is least effective in this type of decompensation, with resulting sudden severe engorgement in the pulmonary vessels. Mack, Grossman and Katz [14] have analyzed the mechanism for dyspnea in pulmonary congestion. They noted the reduced flexibility of the lung due to the distended blood vessels, which assume the rigidity of small pipes. The distensibility of the lung is restored when the congestion is reduced. In this connection it may be stated that, according to studies by Jiminez-Diaz et al.,[15] anaphylactic shock is not bronchospasm but an acute congestion of the lung, with resulting dyspnea similar to that described above.

The bifurcating bronchial trunks are in close proximity to and parallel the bifurcating pulmonary artery. In the deeper recesses of the lung the bronchiolar lumina are soft and readily compressible. Narrowing of the bronchioles is effected by the congested and dilated pulmonary vessels. Wheezes may occur in other conditions of partial obstruction, such as a foreign body or a tumor, or they may be a constant finding of pulmonary emphysema. No muscle spasm is present in these conditions. There is no reason to presume, as stated by Swineford and Magruder,[16] that previous mechanism for wheezes must be established in cardiac asthma, any more than such a mechanism must precede the wheezes of other forms of partial obstruction or emphysema. It seems more logical to ascribe the wheezes to partial obstruction of the bronchioles engendered by dilated vessels than to the view held by Rackemann,[17] that these patients are allergic or potentially allergic.

In an exhaustive review of this subject, Harrison, Calhoun and Harrison [10] concluded that fluid in the bronchi did not cause bronchomotor reflex. No mechanical encumbrance, either within or without the bronchus, appears as a factor in bronchial spasm. This is best illustrated by the emphysematous lung. The wheezes in emphysema are caused by pressure of the dilated air sacs on the bronchiolar lumen, as well as by the tortuosity

of the latter. No spasm occurs and no relief is afforded by adrenalin or aminophylline, as is generally the case in bronchial asthma.

The therapeutic effects of aminophylline may be of some value in comparing bronchial and cardiac asthma. In the cases of bronchial asthma, all but four had definite clinical response. Kallos et al.[18] in their evaluation of aminophylline, found that in guinea pigs there was a greater effect on bronchial smooth muscle than on vascular structures. Young and Gilbert [19] found that aminophylline had a direct dilator effect on bronchiolar musculature poisoned by histamine. It would be difficult to explain this effect on the basis of improved circulatory response as indicated by Osgood.[20] Moreover, the failure of aminophylline to effect relief in cardiac asthma (only four in our 35 cases) is in favor of a mechanical rather than a spasmodic basis for the wheezes. The benefits of morphine in cardiac asthma and its danger in bronchial asthma, as emphasized by Browning,[13] point to a different mechanism for each condition.

Summary and Conclusion

1. Cardiac asthma simulates bronchial asthma but results from left heart failure.

2. "Wheezes" of cardiac asthma result from vascular dilatation and pressure on the bronchi.

3. A–L and A–T circulation times are normal in bronchial asthma and prolonged in cardiac asthma.

4. Principal effect of aminophylline is to relax bronchial musculature.

5. Aminophylline is very effective in bronchial asthma.

6. Aminophylline is of little or no value in cardiac asthma.

7. Aminophylline is of little or no value in left heart failure.

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CASE REPORTS

PROTEINURIA FOLLOWING NEPHRECTOMY AND INTRAVENOUS INJECTION OF LARGE AMOUNTS OF HUMAN PROTEIN *

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Proteinuria can be produced with statistically significant regularity in rats by the reduction of renal tissue to the minimum compatible with life.[4] There is no reason to believe that the human kidney behaves differently from that of the rat, but direct evidence is not at hand, for the experimental methods used in the physiology laboratory on the rat are obviously not applicable to the study of human renal function. The purpose of this paper is to present the findings in a patient from whom, for therapeutic reasons, one kidney was removed, and who immediately thereafter received a large amount of protein in the form of whole blood and plasma, a situation analogous to that of the experimental animal.

Case Report

A 34 year old white man was tranferred from another institution to Halloran Veterans Administration Hospital on November 1, 1947, for the surgical treatment of cirrhosis of the liver. The patient was born in 1914 in Turkey of Greek parentage, and had migrated to Greece in 1921. He was told that during his childhood he was sickly and had fainting spells. Other pertinent history was not available. His father had hypertension, his mother was in a mental institution and one sister had an anemia of undetermined etiology. The patient came to the United States in 1928. From 1937 until his induction into the Army in 1942 he had worked in a restaurant and also as a bartender. During this period he drank heavily, soon averaging about two quarts of whiskey weekly. His diet was presumably adequate, but there were occasional nausea and vomiting after drinking. Shortly after induction into the Army he was hospitalized with bronchopneumonia at Camp Croft, North Carolina, and improved uneventfully. Later in 1942 he had a transient episode of abdominal pain, at which time a medical officer told him that his spleen was enlarged. He served in Italy and, while in Anzio, was hospitalized for a week because of chills and fever attributed to sandfly fever. Hemorrhoids were first noted at this time. Shortly after this illness he noticed aching and stiffness of his leg muscles. He was returned to the United States after 12 months overseas and was hospitalized at Camp Lee in 1944. He was found to have an enlarged liver, two to three fingerbreadths below the right costal margin. Several telangiectases were seen about his forehead, nose and hands, which the patient stated had been present for two years or more. There was mild icterus, with an icterus index of 17. The red blood cell count was 4.3 million; hemoglobin, 13.5 gm.; hematocrit, 44 per cent; white blood cell count, 5,500,

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with a normal differential count. The total serum protein was 7.4 gm. per cent; albumin, 4.2 gm. per cent; the globulin, 3.2 gm. per cent. The cephalin flocculation test was 4 plus. The serum cholesterol was 316 mg. per cent, cholesterol esters, 238 mg. per cent. A hemorrhoidectomy was performed, and the patient was treated with a 2,000 calorie diet, vitamin supplements and liver extract.

He was transferred to the Bronx Veterans Administration Hospital in April, 1945. There his weight was 137 pounds. The liver was enlarged two fingerbreadths and the spleen three fingerbreadths below the costal margin. For the first time an inconstant, faint systolic murmur was heard at the apex. The electrocardiogram was normal. The gastrointestinal series was normal; roentgenogram of the chest showed a slightly enlarged heart. The blood count and urinalyses were normal. The total serum protein was 5.6 gm. per cent; albumin, 2.5 gm. per cent; globulin, 3.1 gm. per cent. The icterus index was 13 to 18. The total van den Bergh was 2.9. The cephalin flocculation tests varied from 0 to 4 plus. The sedimentation rate was 20 mm. per hour (Wintrobe). The oral hippuric acid excretion was 1.7 gm. On a nutritious diet and vitamin supplements, the patient's condition remained essentially unchanged and he was discharged in October, 1945.

The patient continued to have mild abdominal complaints but was able to work in a small radio shop. In March, 1947, the abdominal pain increased and bloating appeared after meals. He had several episodes of chills and fever, with temperature elevations to 104° F. Simultaneously he noted progressive abdominal swelling, necessitating his enlarging both vest and trousers.

He was admitted to Crile Veterans Administration Hospital in April, 1947. The physical findings were: icterus and crepitant basal râles in both lung fields; a blood pressure of 130 mm. Hg systolic and 70 mm. diastolic; a systolic murmur of moderate intensity over the entire precordium, most marked at the apex; ascites; an enlarged spleen, three fingerbreadths below the left costal margin; an enlarged liver, two to three fingerbreadths below the right costal margin; a 3 plus sacral edema, and several spider angiomata over the face and trunk. The laboratory data were: a negative blood Kahn; hemoglobin, 11.5 gm.; a white blood cell count of 7,500, with a normal differential count; a sedimentation rate of 26 mm./hour (Wintrobe); a normal urine; a total serum protein of 5.6 gm. per cent; albumin, 2.4 gm. per cent; globulin, 3.2 gm. per cent; a thymol turbidity of 17; cephalin flocculation tests which ranged from 3 plus to 4 plus; an icterus index of 50; a serum bilirubin of 8.4 mg. per cent, and an inconstant eosinophilia (5 to 7 per cent). The esophagram showed varices. All urinalyses were normal, an intravenous pyelogram revealed no abnormalities. The electrocardiogram was normal. The red blood cell fragility tests were normal. Many malaria smears were negative. Eighteen hundred fifty centimeters of clear yellow fluid were removed by abdominal paracentesis. On one occasion the patient vomited about three ounces of blood. He was sent home on a two month furlough and returned essentially unchanged.

The patient was transferred to Halloran Veterans Administration Hospital in November, 1947, for a splenorenal vein anastomosis. On admission, the pertinent physical findings were: spider angiomata; an enlarged liver, three fingerbreadths below the right costal margin; a spleen palpable three fingerbreadths below the left costal border; a distended abdomen with a fluid wave; a soft systolic murmur heard over the entire precordium, and a blood pressure of 90/65. His weight was 128 pounds.

The roentgen-ray and laboratory data were: hemoglobin, 13.9 gm.; red blood cell count, 4.4 million; white blood cell count, 4,000, with normal differential count; a negative blood Kahn; total serum protein, 6.7 gm. per cent, albumin, 2.9 gm. per cent; globulin, 3.8 gm. per cent; cephalin flocculation test, 4 plus; thymol turbidity, 5.9; van den Bergh, 1.2 mg. per cent direct, 3.8 mg. per cent indirect. The urinalysis

showed a slight trace of albumin and a specific gravity of 1.027, with negative microscopic findings. Two subsequent urinalyses were negative. The roentgenogram of the chest was negative. The electrocardiogram was normal. The bleeding time, coagulation time, clot retraction and Rumpel-Leede tests were negative. Examination of sternal marrow aspirate revealed a normal differential count but a generalized cellular depression. Esophageal varices were again demonstrated.

On January 26, 1948, a splenorenal vein anastomosis was performed by Dr. Arthur H. Blakemore. A markedly enlarged spleen and a moderately enlarged kidney were removed. The surgeon noted a markedly indurated, nodular liver and an apparent increase in the portal venous pressure. During the operation the patient received 4,500 c.c. of whole blood and 200 gm. of human albumin intravenously. There was much bleeding, and at times the patient's blood pressure was unobtainable. The hematocrit value immediately following operation was 14 per cent, the blood pressure, 74/64. On the day following the operation the patient received an additional 1,500 c.c. of whole blood. The hematocrit had arisen to 34 per cent, the hemoglobin to 11.4 gm. and the red blood cell count to 3.6 million. On January 28 the patient received an additional 1,000 c.c. of whole blood. He was febrile for the first few postoperative days, and the icterus index rose to 80 by February 2. Cough, basal pulmonary râles, leg edema and some ascites appeared by February 3. The roentgenogram of the chest on February 10 revealed soft patchy infiltrations at both bases. There was some improvement with penicillin. During this episode the white blood cell count rose to 28,000, with 93 per cent polymorphonuclear cells, the icterus index to 106, the total protein to 6.5 gm. per cent. On January 27, one day after the operation, the urine showed 2 plus albumin, 20 to 25 red blood cells and 8 to 10 white blood cells per high power field, with many granular casts. The blood non-protein nitrogen was 38 mg. per cent. Urinary output remained good. Ankle edema was slight. Abdominal paracentesis on February 17 yielded 225 c.c. of clear yellow fluid. The patient slowly improved; the temperature fell to about 100° to 101° F. A 1 plus edema of the dorsa of his feet continued. In March an eosinophilia (13 to 17 per cent) was noted. No ova or parasites were found in the stools; a rectal punch biopsy was negative. Gynecomastia was first noted at this time. The cardiac consultant found an enlarged left ventricle but did not think there was any valvular or congenital heart disease. The patient's urinary findings on March 29 consisted of constant albuminuria up to 2 plus, granular casts, 10 to 20 red blood cells per high power microscopic field, with a urine concentration reaching 1.018 and 1.020. Late in March the patient began to complain of recurrent transient swelling of the right parotid region. No explanation for this complaint was found.

The patient continued to have slight ankle edema in April. The urinary findings remained unchanged. Temperature had been normal for several weeks. The van den Bergh on April 20 was direct 1.0 mg. per cent, indirect 3.0 mg. per cent; the cephalin flocculation test was 4 plus; thymol turbidity was 9.6 units; the prothrombin time was normal. Pruritus became prominent and was believed to be due to the jaundice. Except for some bleeding from the esophageal varices, there were few significant changes in June and July. In August and September the intermittent episodes of chills and fever reappeared. Occasional injections of Mercurhydrin were necessary.

In December, 25 gm. of human serum albumin were administered daily for five consecutive days. The urinary output of protein increased to 10 and 12 gm. per day (three to four times his preceding daily output). Moderate diuresis was achieved, but the improvement was temporary and Mercurhydrin was reinstituted. During January, February and March, 1949, the patient's condition deteriorated. Edema progressed to involve the thighs and sacrum. Mercurhydrin became less effective. Unexplained chills and fever recurred. Because of persistent anemia (red blood cell

TABLE I

Summary of Urinary Findings

Date	Specific Gravity	Albumin		Microscopic (per high power field)			
		Qualitative	Gm./24 Hrs.	Granular Casts	Red Blood Cells	White Blood Cells	NPN (Blood)
Bronx Veterans Administration Hospital							
4/7/45	1,020	0		0	0	+	11.0
Crile Veterans Administration Hospital							
4/29/47	1,016	0		0	0	2–7	
5/5/47	1,025	0		0	0	1–2	
5/9/47	1,012	0		0	0	+	
5/12/47	1,013	0		0	0	1–2	25.2
5/16/47	1,010	0		0	0	+	
5/22/47	1,010	0		0	0	+	
5/29/47	1,014	0		0	0	1–2	
7/21/47	1,017	0		0	0	2–4	
Halloran Veterans Administration Hospital							
11/3/47	1,027	VFT		0	0	3–4	
11/14/47	1,012	0		0	0	2–3	
11/24/47	1,016	0		0	0	2–3	
1/26/48	Nephrectomy done to accomplish splenorenal anastomosis. On this day, patient received whole blood, 5,500 ml.; plasma, 1,000 ml.; human albumin, 200 gm.						
1/27/48	1,022	+		14–16	0	0	
1/28/48	1,020	+		0	20–25	0	54
1/29/48	1,018	+++		0	20–25	0	39
2/2/48	1,013	++		+++	6–10	3–5	
2/12/48	1,011	++		+++	3–5	6–8	38
2/10/48	1,012	++		+++	3–4	3–4	
3/5/48	1,011	++		0	4–5	1–3	43
3/25/48	1,014	+		+	0	8–10	
3/31/48	1,017	++		+++	0	8–12	
4/9/48	1,012	++		+	3–4	0	
4/28/48	1,010	+		+	2–3	6–8	
5/17/48	1,018	++		++	6–8	0	
6/4/48			2.5				
6/7/48			4.4	+++	6–8	10–12	
6/18/48	1,018	++	2.9	++	14–16	0	
6/25/48	1,019		2.0	+++	6–7	8–10	
7/2/48	1,017	++	1.36	++	1–4	3–6	16
7/14/48	1,010		2.04	+++	4–10	0	
8/6/48	1,012	++	2.24	+++	10–12		
8/23/48	1,010	++	1.92	+++	8–10	5–10	
9/13/48	1,010	+++	1.5	+++	2–3		
10/13/48			3.0				
11/8/48		+++	2.4	+++			
12/23/48	1,010	++++	4.1	++++	10–15	20–30	
12/31/48	1,022	++	2.4	++		2–4	
1/11/49	1,020		2.1	++++			
2/14/49	1,008		2.0	+++	8–10	2–4	
3/7/49		+++	1.8		10–20		

count, 3,000,000; hemoglobin, 10 gm.), a sternal marrow aspiration was performed in February. An erythroblastic marrow with increase in the number of plasma cells was found, consistent with findings described in hepatic cirrhosis.

The Kahn test became persistently positive and was interpreted as a false positive biologic test.

In March the edema increased appreciably and the urinary output of protein rose to 6.8 gm. daily following a mild upper respiratory infection, returning slowly to previous levels with subsidence of the infection.

Urea clearance studies were performed in May and June over six different periods. The average standard clearance was 17.0 c.c. per minute (31 per cent of normal). The determinations were based on a very low urinary excretion rate, ranging between 0.2 and 0.6 c.c. per minute. Although it is difficult to evaluate these results for an oliguric single kidney, they undoubtedly indicate renal impairment.

The patient is still hospitalized. His condition is slowly deteriorating. Further studies are in progress.

The description by the pathologist (Dr. L. Weiss) of the kidney removed at operation reads, ". . . Weighs 185 gm. and measures 13 by 8 by 4 cm. The capsular surface is smooth, glistening, tan, brown in color.

"Microscopic examination of the hematoxylin and eosin stained section of the left kidney reveals the general architecture to be intact. The capsule is thin and essentially normal. The glomeruli are intact. Their basement membranes are not thickened and the epithelial and endothelial cells are present in normal number. There is some granularity of the cytoplasm of the epithelial cells. The glomerular capillaries are normally patent. Bowman's space is of average dimensions. The parietal epithelial cells lining the space are flat. The epithelium of the proximal tubules is markedly swollen and has a granular cytoplasm. The brush borders are almost nowhere visible yet the line marking the junction of brush border and cytoplasm is everywhere intact. The nuclei of these cells are normal. The lumen of the proximal tubules is greatly diminished in size and contains eosinophilic granular and fibrillar material. The thin loop of Henle is lined by flattened cells with scanty granular cytoplasm. Occasionally an eosinophilic hyaline cast fills the lumen of the thin loop. Henle's thick loop is not remarkable except for granularity of the cytoplasm of its epithelial cells. The distal convoluted tubules are not remarkable. The macula densa, where it is seen applied to the vascular pole of the glomerulus, is formed by columnar cells, taller than those of the adjacent distal convoluted tubule, and has a pale cytoplasm, the pallor being more marked toward the basement membrane. The collecting tubules are not remarkable. The interlobar, arcuate and interlobular arteries present minor degrees of intimal fibrous thickening. The afferent and efferent arterioles are essentially normal. Goormatigh's apparatus is in normal limits. The veins contain moderate amounts of blood.

"*Interpretation:* An essentially normal kidney showing changes of so-called parenchymatous degeneration."

Comment

In a sense there were unwittingly performed on a human subject two studies, both comparable to the experiments on nephrectomized animals: first, the effect of a high protein diet on renal size; second, the effect of partial nephrectomy and high protein diet on kidney function. According to Wald,[6] the average mean weight of both human kidneys in the third decade of life is 323 + 6.7 gm. for males. The kidney removed from the patient, a man of less than normal stature

(62 inches in height, 140 pounds in weight), weighed 185 gm., significantly more than one-half of the quoted maximum. As far as could be ascertained by the usual clinical tests, renal function prior to operation and the histologic examination of the removed kidney were essentially normal. A plausible explanation for this enlargement of the kidney may be found in the high protein diet used for four years in the treatment of his cirrhosis. Addis [1] states that the addition of urea to the diet leads to an increase in renal weight which varies with the amount of urea consumed, and, further, that the increase in weight of the rat kidney is due primarily to an increase in urea excretion, and that food differences are chiefly effective insofar as they induce differences in urea excretion. Although urea is the most important factor, Addis points out that some proteins, like casein, have a more profound effect on kidney weight than would comparable quantities of urea. There is no reason to believe that the human kidney does not hypertrophy, like the rat kidney, to increases in dietary protein beyond that needed for maintenance and growth.

In 1932 Chanutin and Ferris [4] demonstrated that, on a standard diet, reduction of renal tissue to a minimum compatible with life produced, in rats, progressive polyuria, albuminuria, nitrogen retention, renal hypertrophy, hypertension and cardiac hypertrophy. Addis and his group [2] have applied this technic most intensively to the study of renal function, and have shown that uremia can be precipitated in young rats following resection of 75 per cent of their renal tissue if a high protein diet is maintained. With a low protein intake, these changes did not develop and the animals survived. Similar studies in rats given intravenous injections of protein led Addis to state that "when patients who have suffered a serious loss of renal tissue are given multiple injections of whole blood and plasma, as not infrequently happens, there may be danger of reproducing the conditions leading to death from uremia." In the patient described in this paper there had been no clinical, radiologic or laboratory evidence of renal disease prior to operation, with the possible exception of increase in renal size. At no time had he shown any significant urinary abnormalities. It is interesting that, within 24 hours of nephrectomy and the parenteral administration of 5,500 c.c. of whole blood, 1,000 c.c. of plasma and 200 gm. of human albumin protein, casts and red blood cells were found in the urinary sediment. Although the conditions in this "human experiment" were not precise and necessarily were not controlled, and, in addition, were complicated by shock, blood loss, anesthesia and protein disturbances associated with an underlying cirrhosis of the liver, there seems to be a suggestive parallel between the postoperative findings in this case and the findings described in nephrectomized rats on excessive protein intake.

Elevation of renal vein pressure acting in conjunction with the above described mechanism, or perhaps operating as the primary factor in producing the proteinuria, was considered. It has been known clinically for some time that a reduction of renal blood flow following renal vein obstruction is associated with proteinuria.[5] Bradley and Bradley [3] applied pressure to the anterior abdominal wall of normal subjects by means of a pneumatic girdle inflated to 80 mm. Hg and were able to produce a rise in renal vein pressure from the normal 6 to 7 mm. Hg to 18 to 20 mm. Hg. With this rise in venous pressure, protein appeared in the urine in variable amounts. On most occasions the proteinuria was not striking, although it occurred regularly. It is conceivable that the splenorenal vein anasto-

mosis in this patient effectively transferred the portal vein hypertension to the renal venous system, with the resultant proteinuria. This possibility is now being investigated by more quantitative means.

The existence of proteinuria in a patient requiring large amounts of protein for his underlying disease created interest in the possible effect of varying levels of protein intake on the proteinuria. Accordingly, the patient was placed for weekly intervals, in sequence, on a 70, 50 and 20 gm. protein diet. Daily 24 hour protein excretion was measured. (See figure 1.) In general, the quantity of protein excretion decreased with the decrease in protein intake.

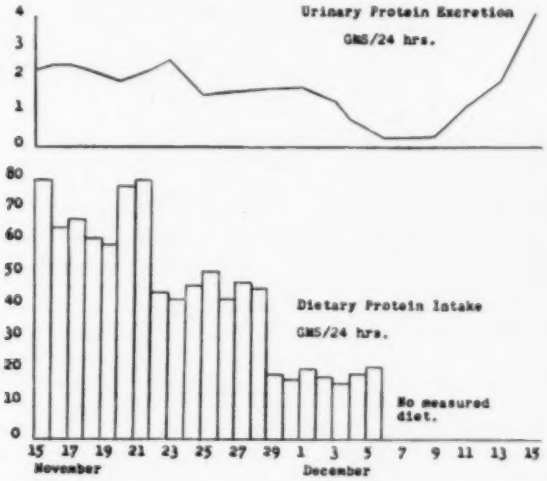

FIG. 1. The effect of dietary protein on urinary protein excretion.

SUMMARY

1. A case is presented in which significant proteinuria appeared following nephrectomy and large amounts of parenteral protein.

2. The findings resemble those in partially nephrectomized rats on excessive protein intake.

3. Attention is directed to the possible danger of massive transfusions and the excessive administration of protein parenterally, especially following nephrectomy.

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ACCESSORY LOBES OF LIVER AND THEIR SIGNIFICANCE IN ROENTGEN DIAGNOSIS *

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ANOMALOUS or accessory lobes arising from the right lobe of the liver are rare but, when present, give rise to diagnostic problems that must be solved. Only a small number of such cases have been reported. Roques and Sohier [4] and Hardisty et al.[2] presented individual cases in which deformity of the right dome of the diaphragm was found on routine x-ray examination of the chest. In each case the patient was asymptomatic. In each instance pneumoperitoneum revealed a smooth mass arising from the superior surface of the liver. One (Roques and Sohier) was diagnosed echinococcus cyst, the other (Hardisty et al.) benign tumor or accessory lobe of the liver. At operation, both were found to be accessory lobes arising from the upper surface of the right lobe of the liver. Roques and Sohier reported two similar cases from the French literature. Kornblum and Stephenson [3] reported such a case, proved at autopsy, in a six months old female who died of a septicemia and bronchopneumonia. During life, a smooth dense shadow on a roentgenogram of the chest was interpreted as being due to an interlobar empyema.

Friedman, Solis-Cohen and Levine [1] reported such a case in a year old female, and discussed the diagnostic importance of pneumoperitoneum.

CASE REPORT

A 61 year old white female complained of alternating diarrhea and constipation of four months' duration. She would have three to four watery stools daily for three to seven days, followed by constipation lasting one to two days. No blood, pus or mucus was noted in the stools. Her present illness was associated with abdominal distention without nausea, vomiting, fever or chills. A loss of eight pounds had occurred.

Physical examination: Dullness to percussion and diminished breath sounds over the right lower lobe posteriorly were the only significant physical findings.

Laboratory findings: Wintrobe (corrected) blood sedimentation rate was 29 mm. An achlorhydria with a total gastric acidity of 14 degrees was found. No anemia or eosinophilia was present. Stools were negative for occult blood, ova and amebae on five examinations.

Roentgen examination revealed normal gastrointestinal and urinary tracts.

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FIG. 1. Postero-anterior chest shows a large dense mass with smooth surface occupying the right cardiophrenic angle. Lateral projection following pneumothorax demonstrates the mass to lie below the right diaphragm. The surface is smooth, and the outline is continuous with that of the superior surface of the liver.

Fluoroscopic and roentgenographic examination of the chest revealed a large rounded smooth tumor mass in the right lower lung field posteriorly, with obliteration of the right costophrenic sulcus. The posterior half of the right diaphragm was elevated slightly, lagged during respiration and moved paradoxically on forced respiration.

Three hundred fifty cubic centimeters of air were then injected intraperitoneally. Films in expiration and inspiration in the upright position revealed the mass, which measured 7 by 10.5 cm., to be subdiaphragmatic, with a pocket of diaphragm extending over but definitely separated from and not adherent to the mass. Following this examination, a transthoracic exploratory operation was performed to rule out a tumor of the liver. A tumor mass, approximately 15 cm. in diameter, firm in consistency and covered by a thin fibrous layer of diaphragm, was found attached to the right lobe of the liver by a pedicle measuring approximately 10 cm. in diameter. Aspiration failed to produce any fluid. The mass was then excised and the diaphragm repaired. The diaphragmatic defect appeared to be of congenital origin, with hepatic protrusion with constriction of the neck of the tumor mass at the diaphragm level and enlargement above that level.

The gross pathologic specimen consisted of a 12 by 6 by 5.5 cm. mass of soft, rubbery consistency with a smooth, bluish-gray membrane. The cut surface was smooth, glistening and reddish-brown in color, and presented a lobulated appearance consistent with normal hepatic tissue. The microscopic pattern showed slightly larger than normal liver lobules, and small portal spaces with generalized underdevelopment of the bile duct system. The microscopic appearance was that of functioning liver.

The final diagnosis was segmental eventration of the right diaphragm with an accessory lobe of the liver. On a regimen of dilute hydrochloric acid the patient's symptoms cleared completely.

Discussion

The cause of anomalous lobes of the liver is unknown. It has been stated that the lobes of the liver grow along the course of the different embryonic veins, and that anomalous lobes may be the result of an extra branch of a vein.

In the differential diagnosis of such a lesion, the history and physical and laboratory findings are of paramount importance. Gummas should be associated with a positive serologic test for syphilis and clinical evidence of syphilis. Inflammatory lesions should be accompanied by a history of a febrile illness. Echinococcus cysts should be suspected in the presence of a positive complement fixation test and an eosinophilia. Malignant or benign tumors remain difficult if not impossible to differentiate. Pneumoperitoneum remains the fundamental procedure to differentiate between a lesion of the diaphragm, an intrathoracic tumor and a lesion of the liver, but it does not offer a means of differentiation of tumor or accessory lobe of the liver, which may be done only by macroscopic or microscopic examination. If a liver abscess is causing protrusion of the diaphragm, adhesions are usually present, preventing the entry of air into the subdiaphragmatic space.

Summary

A case is reported of anomalous lobe arising from the superior surface of the right lobe of the liver found coincidentally during a gastrointestinal examination.

While the presence of such a lobe is rare and of no consequence per se, in most cases its differentiation from clinically significant lesions is necessary.

Pneumoperitoneum is of value in determining whether the lesion is within or above or below the diaphragm, but offers no means of identifying either tumor or accessory lobe.

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BLINDNESS FOLLOWING MASSIVE GASTRO-INTESTINAL HEMORRHAGE *

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Few physicians encounter blindness as a complication of severe hemorrhage. First-hand experience with this dramatic and disastrous complication is vividly remembered. Since the medical literature contains few accounts of this complication, the following case is reported.

Case Report

A conscientious 45 year old factory maintenance engineer held a very responsible position during World War II and was under severe nervous strain. On June 16, 1946, he attended a party and had several cocktails. The following day he had some mild indigestion but continued to work. On the morning of June 18 he awoke feeling weak, clammy and thirsty. At 9 a.m. he passed a tarry stool. When he was first seen shortly after, immediate hospitalization was advised. The patient demurred but that afternoon was hospitalized. His past history included several mild attacks of asthma but no indigestion, alcoholism or other symptoms of any kind.

Shortly after admission to the hospital the patient vomited 600 c.c. of bright red blood, and later had a second large, unmeasured hematemesis and went into shock. He received 1,000 c.c. blood immediately and recovered from shock in about two and one-half hours. He had another tarry stool and at the end of his first hospital day seemed to be in good general condition.

On the second day the patient ran a high fever which was believed to be associated with the transfusion. His blood was Type IV, Rh positive, and only similar blood was used after proper cross-matching. However, because of the apparent febrile response, it was decided to give blood cautiously, since more harm than good might ensue from too rapid replacement associated with transfusion reactions. To enhance his hematopoietic activity, he was given parenteral liver and iron daily. During his second hospital day the patient went downward badly; he had six tarry stools and

* Received for publication March 24, 1950.

became progressively weaker, and that evening developed Cheyne-Stokes respiration and almost died. He was given another transfusion of 500 c.c. whole blood at this point and rallied considerably.

On the third day his temperature curve spiked again and it was again felt that this was a transfusion reaction. Since his general condition was improving, no more blood was given until the fifth hospital day. That evening the patient first noticed some blurring of vision. For this reason, the atropine which he had hitherto been receiving was discontinued. A blood count on the following day revealed the fol-

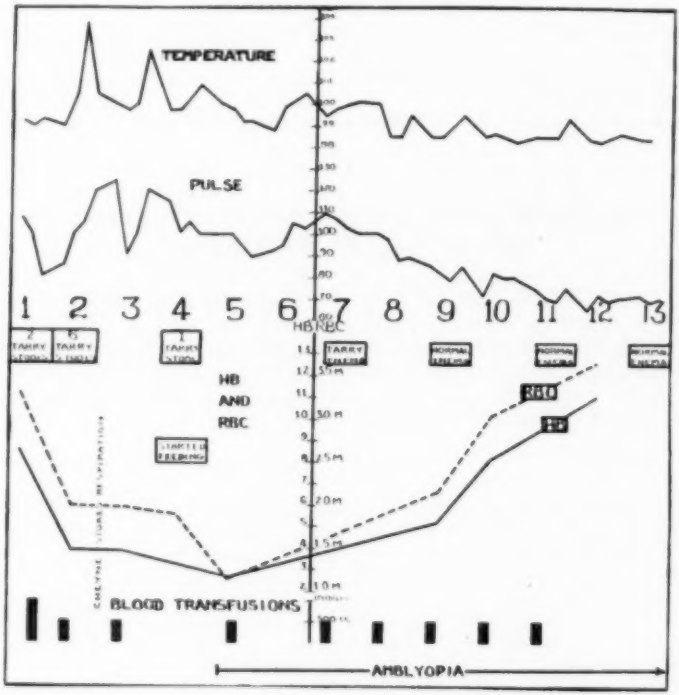

FIG. 1. Chart of patient's course in the hospital. The abscissae indicate time in days. The ordinates from top to bottom indicate temperature, pulse, nature of stools, blood counts, amount of blood given and visual disturbance.

lowing: red blood cells, 1,120,000; hemoglobin, 2.55 gm.; reticulocytes, 4 per cent. and much polychromasia, stippling, anisocytosis and poikilocytosis of the red blood cells. The patient's vision was now deteriorating, and on the seventh day daily blood transfusions were given and continued until the patient had received 5,000 c.c. blood. The laboratory findings and clinical course are outlined graphically in figure 1.

Ophthalmoscopic consultation with Dr. Malcolm Johnson was obtained on the eighth hospital day. It was found that the patient could not count fingers but could recognize movement at eight inches. The pupils were dilated and reacted sluggishly to light. The media were clear. The discs were pale, and mild edema of the borders

was seen. The vessels were normal in size. There was a slight perivascular seepage in the inferior temporal quadrant near the disc border of the right eye. Both macular areas were normal and the retina was pale. These findings remained essentially unchanged during his subsequent course. He left the hospital on July 1, 1946, in good general condition but quite blind.

Since that time the patient has been cared for and observed on numerous occasions. He has enjoyed good general health and has accepted with remarkable equanimity the tremendous psychologic impact of his blindness. He was optimistic at all times and insisted that he was continually improving, although objective observations from time to time failed to confirm this. A determined search for the source of bleeding was made. The entire gastrointestinal tract and colon were studied roentgenologically on several occasions, the first examination being made in

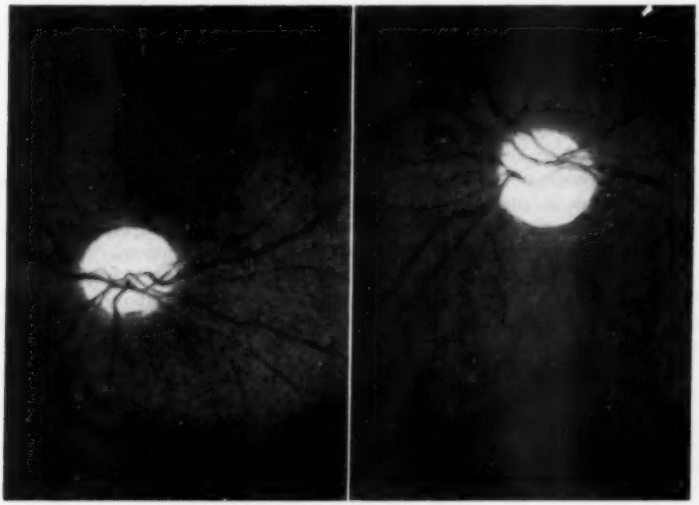

FIG. 2. Both fundi taken three years after the massive hemorrhage.

August, 1946. Yearly roentgen-ray studies have failed to reveal any abnormalities. The patient was reëmployed by his firm in the packing department at a much smaller salary and has led an active life within the limitations of his blindness. His vision gradually improved during the three ensuing years until he was able to play cards and golf, but he is not as yet able to read. He has been seen on many occasions by Dr. Ralph Tanner, whose observations three years after the onset of blindness may be summarized as follows: Vision in the right eye had improved to ability to count fingers at two feet. This was possible with the left eye at six feet with greater accuracy than ever before. Visual fields were approximately one-half normal size and central vision was essentially gone. The optic nerve heads were chalky white. There was no sheathing of the vessels, although some were attenuated and the macular retina and parts of the periphery showed shiny degenerative freckles.

Treatment at the outset consisted mainly of supportive measures. Food was withheld until it was felt that excessive bleeding had subsided. The patient was then started on frequent feedings of milk and cream, aluminum hydroxide, phenobarbital

and atropine, and this was gradually modified as the clinical condition of the patient changed. He was kept on a modified ulcer management for six months after his discharge from the hospital, and has since eaten all foods that he likes without indigestion. At the beginning he was given large doses of nicotinic acid and thiamine hydrochloride parenterally, and this was continued by mouth for a period of six months following his discharge from the hospital. In addition, he has taken Squibb's Therapeutic Formula capsules twice daily for almost four years.

Discussion

Blindness following hemorrhage has been reported infrequently in the ophthalmologic journals. There is a paucity of information on this subject in medical journals, systems of medicine, textbooks of medicine, etc. A recent review of gastroenterologic literature [1] fails to mention reports on this condition. Two excellent sources of information at the present time are Duke-Elder's Textbook of Ophthalmology,[2] and a recent survey article by Hollenhorst and Wagener.[3] The pertinent literature is covered in great detail, and the reader is referred to these sources to amplify the short summary of these articles which follows.

Posthemorrhagic blindness has been known since Hippocrates, and to date about 300 cases have been reported. It occurs most commonly from gastrointestinal hemorrhage, but is also associated with hemorrhages in parturition, pulmonary tuberculosis and other medical conditions. It is rarely associated with hemorrhages from wounds. It occurs more often from small repeated hemorrhages than from large ones, although the amount of blood loss may be the same. Blindness is usually bilateral but may be unilateral, and usually begins three to seven days after large hemorrhages. It occurs slightly more often in women, but permanent blindness is more common in men. It has been reported at ages ranging from two years to 77. Approximately 50 per cent of patients so afflicted are permanently blind and, of those who recover, only 10 to 12 per cent recover completely.

Eye findings include dilated and fixed pupils, attenuation of retinal vessels and a white disc. Retinal hemorrhage, edema and a macular cherry-red spot are frequently seen. Complete optic atrophy occurs in the worst cases, and some pigment disturbances of the retina are common. The phenomenon is occasionally associated with signs of cerebral anemia, aphasias, deafness, nystagmus, polyneuritis or coma. The essential pathology is a preferential degeneration of the third neuron and resembles in many respects the picture seen in methyl alcohol or quinine poisoning.

The cause of the condition is not clear. Most writers are not willing to explain the blindness on an ischemic basis alone. The following factors have been suggested as causal: (1) hemorrhage into nerve sheaths; (2) ischemic fatty degeneration of the optic nerve; (3) retinal circulatory stasis; (4) low blood pressure; (5) lack of oxygen with retinal vessel spasm; (6) a combination of anemia, reduction in blood volume, dilution of blood with tissue fluids and concomitant lowering of plasma proteins, and (7) toxins of various kinds, such as a "severe hemoclastic shock or anaphylactic crisis or a toxemia due to profound hemolysis." [2]

Recommended treatment consists of rapid restoration of blood. Paracentesis of the eye has been recommended to lower intraocular pressure in an attempt to improve retinal circulation.

Applying these considerations to the case in hand, it would seem that it is similar to the cases previously reported and that the clinical findings tally with those described in the literature. It is a difficult matter definitely to ascribe a cause that would tally as well with the theories proposed above. It is quite plausible that the large blood loss and resultant anemia may have, per se, caused sufficient damage to retinal cells to cause blindness in this patient, and this would seem the most likely explanation. The absorption of large amounts of partly digested blood may also be a factor which might have been more fully investigated. Preoccupation with supportive measures and inexperience with this condition precluded studies which might have shed some light on the cause of this phenomenon.

The management of this patient is not by any means presented as a model, and there are some changes which the author would make if again confronted with a similar case. However, under any system, the management of such a case is difficult. Welch [4] has summarized the results of treatment of massive gastroduodenal hemorrhages at Massachusetts General Hospital over a 10 year period. He selected only those cases which went to 2,500,000 red blood cells and 7 gm. hemoglobin or less, and collected statistics on this group. He states, "Bleeding that continues massively and persistently after entry to the hospital has been almost uniformly fatal in this institution," and recommends admission of the patient to a surgical ward for the first three days so immediate surgery may be accomplished if this seems necessary. No incidence of blindness was encountered in this series. There is strong evidence presented in this paper to conclude that this patient should have had surgical exploration on entry to the hospital, and it may well be that a gastric resection in the last analysis would have saved his vision. Ocular paracentesis might also have been considered. A more rapid replacement of the blood loss might also have changed the course of the disease.

The peculiar reactions following the transfusions prompted an investigation of the donors. The second donor subsequently developed a furunculosis which lasted several months, and the blood bank finally refused to take blood from him. He subsequently recovered completely. This donor was not subject to eye disease. The rest of the donors had had good health since 1946. The patient's blood was retyped and found to be Hr and Rh positive, so no antibodies for these factors could have been present. He was also type "O." This tallied with determinations made in 1946.

Summary

A case of massive gastrointestinal hemorrhage followed by blindness is presented. The exact source of hemorrhage was not determined. The patient went into deep shock and had Cheyne-Stokes respiration at one point, and his hemoglobin went to 2.55 gm. Five days after the onset of this condition the patient developed blindness which was permanent and characterized by loss of central vision. The patient was observed for three and one-half years following the hemorrhage. The exact cause for this phenomenon is not known.

Acknowledgment

The author wishes to thank Dr. Ralph Tanner for his great aid and counsel in preparation of this paper and in facilitating the making of fundi photos in the Stanford Ophthalmology Department.

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POPLITEAL ANEURYSM DUE TO SYPHILIS: REPORT OF A CASE*

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ALTHOUGH aneurysms of the popliteal artery are not too frequently seen, this vessel is the most common site for peripheral aneurysm formation. The chief cause of aneurysm of the vessels of the lower extremity is arteriosclerosis; Allen, Barker and Hines,[1] in their textbook, state that this is indeed almost the only cause in individuals over 60. They also note less common causes, such as mycotic arteritis, necrotizing arteritis and trauma. They state that syphilis as a cause of aneurysm in the lower extremity is rare.

The segment of the popliteal artery which is at the level of the femoral condyles is peculiarly liable to degenerative disease. The exposed, ill-supported location of the artery, its relation and attachment to the posterior femur, the constant flexion of the knee joint with resulting strain and kinking of the vessel, the pressure changes associated with bending, lifting and straining, all appear to help weaken the arterial wall at this point. There is also, for the above reasons, a predilection for these aneurysms to be subject to rupture and formation of a secondary false sac, often from trivial trauma.

In perusing the available literature on these aneurysms, certain repeated observations are noted. Arteriosclerosis is frequently stated to be an important predisposing factor. Trauma, however, direct or indirect, is often credited with playing a definite part in the final picture. Many of the case reports state that the patient is a Negro with positive serology and a positive history of luetic infection. Syphilis is thought to be an important etiologic agent by some but is quickly discarded by others. Lucke and Rea,[2] in a statistical study of aneurysms of the larger vessels in 1921, reported that aneurysm is much more frequent in males than in females, in a ratio of 4.2: 1, and that it is more frequently found in the Negro than in the white, and at an earlier age. Although these statistics included only aneurysms of the central vessels, the findings appear to apply to popliteal aneurysms as well.

* Received for publication March 24, 1950.
From the Medical Service of Dr. E. L. Shlevin, Jewish Hospital, Brooklyn, New York.

It is almost impossible to find a well-documented case of syphilitic aneurysm of the popliteal artery. Theis [3] states that "peripheral arterial aneurysm is no longer considered the result of luetic infection." Of eight cases operated upon, Theis reported a history of syphilis in only one. The Wassermann tests in that patient were negative. There was no evidence of luetic change in the operative specimens. Yater,[4] however, reported four cases of ruptured popliteal aneurysm, stating that "syphilis and arteriosclerosis are the common etiologic agents of the non-traumatic variety of aneurysm." In all four of Yater's cases the patients were Negroes; pathologically, the lesions in all four cases were nonspecific. However, all gave a history of a primary lesion and the serology was positive in three. Although he admitted that the above facts did not prove the diagnosis of syphilitic aneurysm, he felt, in spite of the nonspecific pathology, that it was highly probable that these lesions were luetic. He suggested that syphilis might produce lesions other than those usually ascribed to the disease. Wells, Coburn and Walker,[5] in discussing a case of popliteal aneurysm which they reported in 1936, state the following: "The statistics of Stokes, Garland and Lucke and Rea reveal syphilitic aneurysms as being far more common in larger arteries. However, in spite of an appalling lack of histologic proof, the frequency of 4 plus Wassermann tests associated with popliteal aneurysms leaves little doubt as to the importance of this etiologic agent." In a review of 35 cases of popliteal aneurysm taken from Guy's Hospital Reports from 1836 to 1893, Harley [6] concluded that trauma seemed to play an important part in 57 per cent of the cases, and that arteriosclerosis and alcohol also were significant factors. He felt that syphilis seemed of relatively less importance as a causative factor. Syphilis was definitely stated to be present in only one of his cases, and a probability of this disease existed in two others, but no histopathologic studies were reported. It is to be noted that Wassermann and Kahn reactions were unavailable at the time that most of these cases were recorded. Matas [7] who had much to do with developing the surgical treatment of aneurysms, states in speaking of popliteal aneurysm that "a history of syphilis, alcohol and other causes of arterial degeneration is frequently present." Barker,[8] while reporting a case in 1934, reviewed 30 cases taken from the literature of the preceding 20 years and found that 13 of these had occurred in syphilitics. Other causes mentioned for the remainder were trauma in nine, arteriosclerosis in seven, and mycotic embolus in one. Barker goes on to observe, however, that the basis for the consideration of syphilitic arteritis as the cause may be questioned in many of these cases, as it consisted simply in the fact that comparatively young men with strongly positive blood Wassermann reactions had aneurysms. In only one of these 13 cases were histopathologic studies made to confirm the diagnosis. In these 30 cases all the patients were males.

It may be assumed, therefore, that proved syphilitic aneurysm of the popliteal artery is very rare. Although microscopic study of the operative specimen in the case reported below revealed no spirochetes, the pathology of the arterial wall was so typical of the inflammatory reaction seen in syphilis that it was decided to report this case as such.

Case Report

This 60 year old male colored laundry worker was first seen at the Jewish Hospital Clinic in September, 1948, because of pain in the left popliteal area. The patient

had been well until early September, at which time he first noticed pain in the back of his left knee. There was no history of trauma. Examination at that time revealed a "small tender mass in the left popliteal space." Roentgenogram of the region was requested. He felt better for a while, although with intermittent pain, until about four months later, when the symptoms increased. The patient was again seen in the medical clinic. At this time there was first noted a "pulsating mass in the left popliteal area, moderately tender to pressure." A bruit was heard over the popliteal artery and the left dorsalis pedis pulsation was diminished. The temperature of the left lower extremity was colder than the right. Roentgenogram of the chest was negative except for some evidence of slight aortic dilatation, but no true aortic aneurysm was seen. Roentgenogram of the left knee showed a soft tissue mass in the popliteal space at the level of the femoral condyles. It was noted that "this might be consistent with the diagnosis of Baker's cyst but aneurysm cannot be excluded." Angiographic studies were suggested. The clinic electrocardiogram showed a tendency to right axis deviation and an isoelectric T_1 and T_2. The V.D.R.L. was positive in a titer of 1/32, and a Wassermann test gave a 4 plus reaction. A diagnosis of aneurysm of the left popliteal artery was made and the patient was admitted to the medical ward.

On admission the patient complained of severe left popliteal pain, which he said had been extremely intense since his last clinic visit. It appeared that this aggravation of his symptomatology dated from a diagnostic needling which had been performed in the clinic at that time. The pain was so severe that it interfered with ambulation and kept him in bed. It was described as throbbing and burning, and radiated down the left posterior calf. The patient also stated that his left foot seemed colder than the right and that there was associated numbness and tingling of the left lower extremity. The patient had worked in the hospital laundry pushing laundry trucks, but there was no history of direct trauma to the left knee. The remainder of his history was unremarkable; he denied any knowledge of syphilitic infection in the past, and gave no history of primary or secondary lesions.

The pertinent findings on physical examination were limited to the left lower extremity. The blood pressure was 160 mm. Hg systolic and 88 mm. diastolic. The left popliteal region presented a tender, tense, pulsating fullness. A definite systolic thrill could be felt over the mass, and on auscultation a definite systolic bruit, rough in character and of moderate intensity, could be heard. This bruit was not transmitted along the course of the femoral or tibial vessels. It could not be obliterated by pressure because of the tenderness of the mass. There were no remarkable color changes on positional maneuver of the limbs. The left dorsalis pedis and posterior tibial vessels were not palpable, although those on the normal side were easily felt. The left foot was cooler than the right. There was a mild degree of edema of the left leg and foot. No obvious trophic changes were present.

Oscillometry showed normal readings at all levels on the right side. On the left, the reading over the popliteal space was markedly exaggerated; the reading over the left tibial level was markedly diminished to levels indicative of practically no flow through the tibial vessels, and the reading across the left foot was merely a "flicker." Skin temperatures taken with the thermocouple, however, were well above the normal limits on both sides in the feet and toes, and equal to within 1 to 2° F. The reading over the left knee was excessively high, 93° F., as compared with 89.5° F. over the normal side. These findings were compatible with the diagnosis and with the pattern of an increased skin collateral about the left knee joint bridging the mass and adequately supplying the extremity below the popliteal obstruction. Figure 1 illustrates the oscillometric and skin temperature readings, as well as the location of the tumor.

The laboratory data on admission were as follows: The red blood cells were 3.63, the hemoglobin 74 per cent, the white blood cells 7,350, the differential normal. The

sedimentation rate was 62 mm. (Westergren). The urine was negative. The blood sugar and urea nitrogen were normal. The serology was reported as follows: V.D.R.L. positive, V.D.R.L. titer 1/16; Wassermann 4 plus, Wassermann titer 1/16. The spinal fluid Wassermann was 3 plus.

A diagnosis of popliteal aneurysm was made; one could not say whether this was arteriosclerotic or syphilitic, in spite of the serologic findings. The possibility of rupture of the aneurysm with formation of a secondary false sac was also entertained.

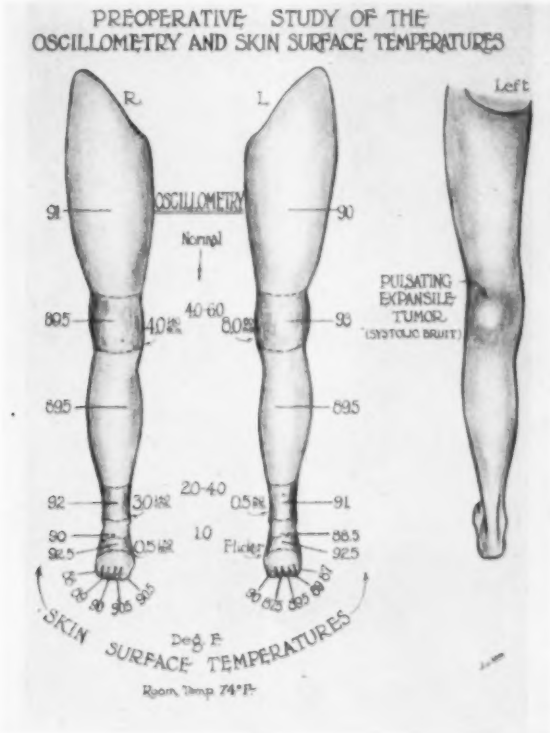

FIG. 1.

particularly in relation to the diagnostic needling. It was felt that with the slowly advancing obstruction of the popliteal artery in this particular aneurysm, adequate collateral channels were able to develop by the time the distal flow was impaired. Evidence for this was shown by the high skin temperature over the left patella, as compared with that on the normal side, and normal skin temperatures in this extremity in spite of almost absent oscillometry. The edema present was interpreted as being due to pressure on the popliteal vein, and the paresthesia and tingling in the leg to pressure on the tibial nerve.

An arteriogram (figure 2) showed confirmatory evidence of arterial aneurysm.

This demonstrated that the popliteal artery ended rather abruptly at the upper pole of the visualized mass, while a network of small collateral vessels could be seen to carry the diodrast around the periphery to enter the arterial circulation of the lower leg. There was no filling of the veins.

FIG. 2. Angiogram of femoral and popliteal artery, showing aneurysm and collateral circulation.

On the basis of these studies, it was felt that it was possible to operate upon the lesion without fear of embarrassment of the circulation of the distal limb. The patient was then transferred to surgery.

Report of Operative Findings and Procedure: A longitudinal incision was made, about nine inches in length, "S"-shaped, going transversely through the popliteal fold. The skin and superficial fascia were reflected, exposing the deep fascia of the popliteal space. The lesser saphenous vein was identified and ligated. The upper portion of the deep fascia was opened and the popliteal space entered above the aneurysmal

sac. The hamstring muscles were retracted, and the dissection was advanced to the adductor canal, where the lower femoral artery, vein and tibial nerve were exposed. The medial geniculate vessels were identified and ligated to permit better development of the artery and vein. The tibial nerve was carefully reflected mesially. The popliteal artery was liberated from its sheath and two umbilical tapes passed under it. Traction upon these tapes arrested the pulsation of the aneurysm and caused cessation of the bruit. The afferent artery to the sac now under control, the fascia over it was opened longitudinally. A dull-gray, spherical, pulsating, compressible mass presented in the wound (figure 3). With traction on the umbilical tapes, the sac was opened longitudinally for a distance of two inches. A large quantity of laminated slate-gray organized hematoma, as well as a moderate amount of fresh red thrombus, was contained within the sac and was evacuated. The floor inside the sac

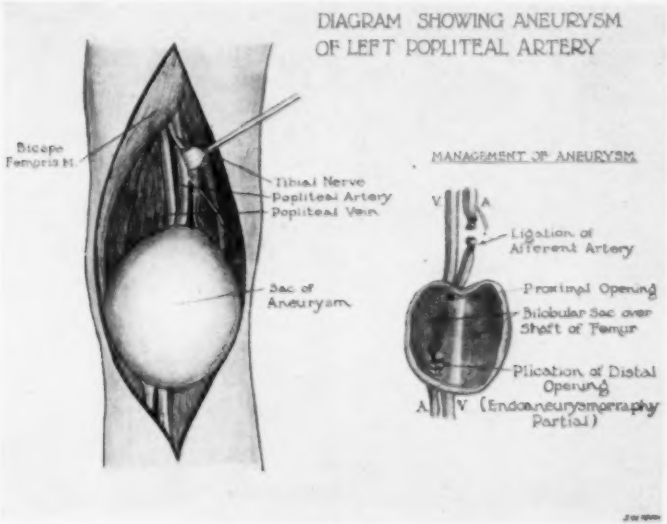

FIG. 3.

was white and glistening, without evidence of atheromatous change or wrinkling. It was adherent to the underlying periosteum of the femur, dumb-bell in shape, with equal-sized cusps lying over the bone. The afferent and efferent openings into the sac lay on the mesial side and were funnel-like in shape. Probes passed through these openings entered the respective segments of the popliteal artery. Upon release of the tapes a free flow of blood issued from the afferent artery.

Because of the friability of the sac wall, it was not deemed advisable to perform a classic endoaneurysmorrhaphy. The afferent artery was therefore doubly ligated about two inches proximal to the sac with braided black silk. Upon completion of this procedure it was observed that the sac filled moderately with blood through the distal opening. This opening in the sac was then closed by plication with three interrupted black silk sutures.

The nonadherent redundant leaflets of the sac wall were removed and sent for histologic study. The remainder of the sac was left in situ so as not to interrupt any

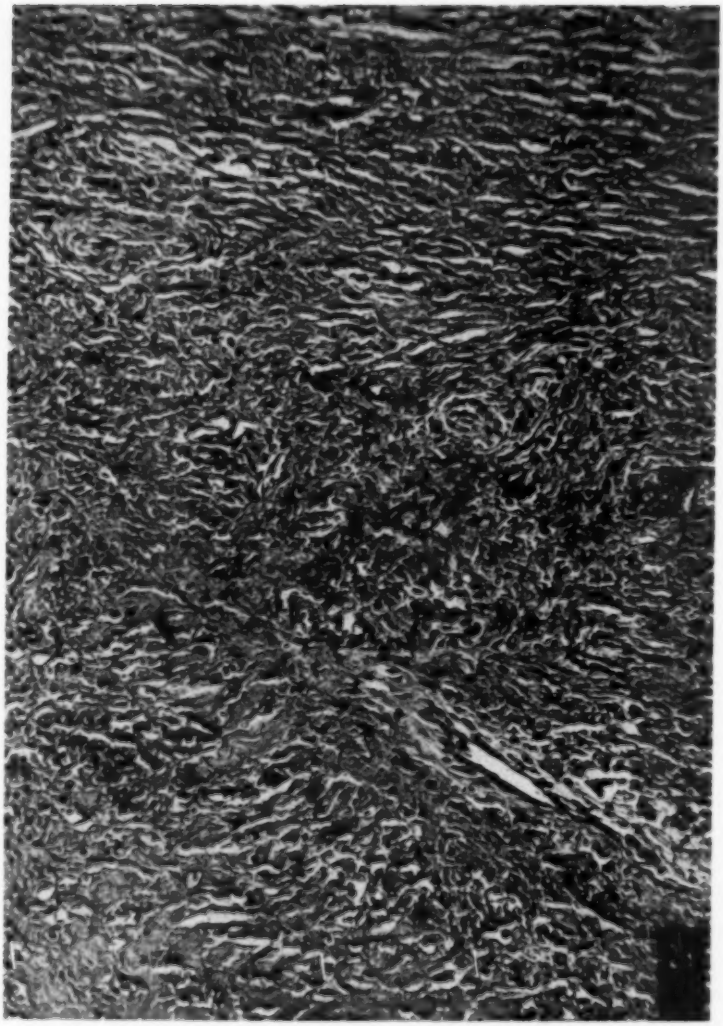

FIG. 4. Section showing cellular infiltration of aneurysmal wall (H & E stain ×700).

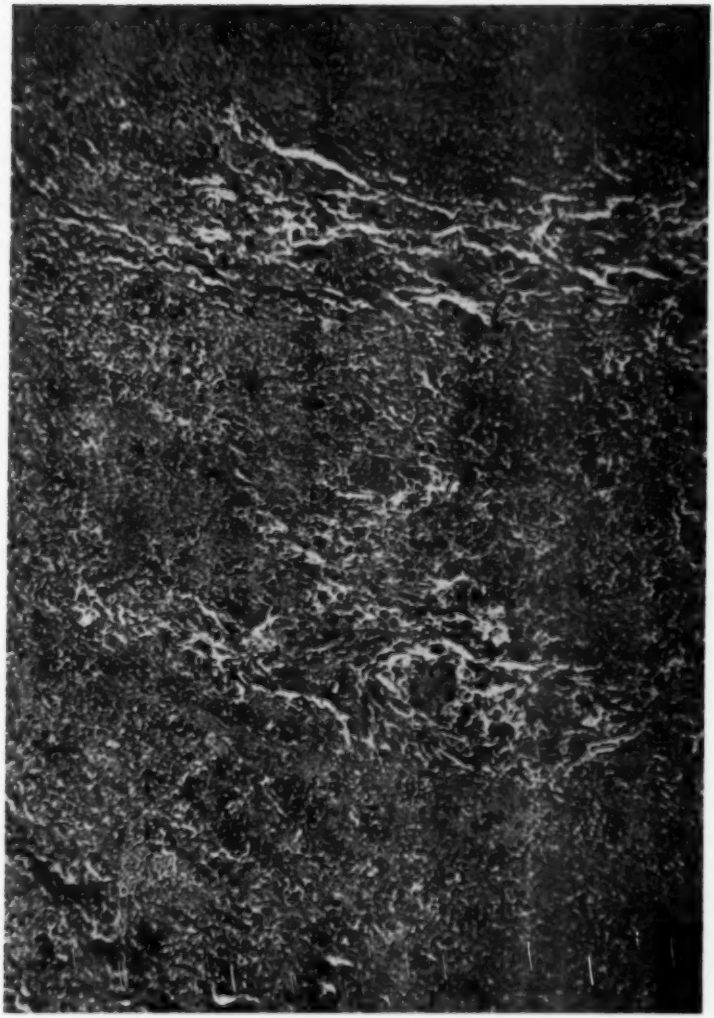

FIG. 5. Section through wall of aneurysm to show fragmentation of elastic tissue (elastic tissue stain × 700).

possible collateral channels. The popliteal vein was not ligated. After six minutes of observation the wound was dry. Closure of the fascia and skin was performed with interrupted black silk sutures.

Pathologist's Report: "The specimen consists of several portions of soft pink tissue, the largest measuring 6 by 5 by 4 cm. The largest fragment contains recently clotted blood. The wall is made up of layers of red-brown soft material."

Microscopic Findings: "A preparation through the wall shows all the features of a luetic infection; within the serosa and in the media there are many engorged vessels and small foci of freshly extravasated blood. The arterioles show a proliferative endarteritis and the cellular infiltrate consists chiefly of plasma cells. There are also small foci of necrosis in the media and some fragmentation of the elastic tissue."

The pathologist reported the specimen as "wall of popliteal arterial aneurysm, probably luetic." Figures 4 and 5 are photomicrographs of the aneurysmal wall.

Course: The patient's convalescence in the hospital was uneventful. During this time he received a course of intensive antiluetic therapy. There were some numbness and tingling in the distal half of the foot and toes despite lack of evidence of angiospasm. The foot remained warm and normal in color. It was felt that the paresthesias were due to manipulation of the tibial nerve during operation. These gradually became less intense and were felt only in the tips of the toes at the time of discharge. He was able to walk without a limp or intermittent claudication. No keloid formed at the site of the scar and the popliteal space was soft and free.

Summary

A case of popliteal aneurysm due to syphilis is presented. This was treated surgically with excellent results. Histopathologic study of the aneurysmal wall was done and is herein reported.

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ANGINA PECTORIS IN THE ABSENCE OF CORONARY DISEASE *

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THE diagnosis of angina pectoris in the overwhelming majority of instances implies significant disease in the coronary arteries. In fact, it is usual to find at least one thrombosis in a coronary artery when cases of classic angina are examined post mortem. This correlation has been very well established by the clinical-pathologic studies of Blumgart and his co-workers, using their improved technic of visualizing the coronary vessels.[1, 2] However, there is a group of conditions in which anginal pain occurs where other mechanisms are invoked that are regarded as explaining or producing angina. It is sometimes thought that these conditions may cause angina pectoris even in the absence of coronary artery disease. When they occur in older individuals one can always suspect, unless careful pathologic proof to the contrary is available, that significant coronary artery disease is also present, and that the other factors merely bring to light the anginal state. The conditions referred to above are thyrotoxicosis,[3] anemia,[4, 5] paroxysmal rapid heart action [6] and valvular disease. Well-documented instances of aortic stenosis,[7] aortic insufficiency or mitral stenosis with angina pectoris [8, 9] have been published in which careful postmortem examination of the coronary arteries failed to show any significant alterations in these vessels. There has been a paucity of detailed reports of angina with normal coronary arteries in other conditions.

It is common knowledge that certain patients with severe anemia may have anginal pain when the hemoglobin level of the blood falls to low levels, and be free from angina, or comparatively so, when the hemoglobin level is elevated toward normal. However, this is generally observed in older individuals, in whom there is reason to believe that the coronary arteries are also abnormal. Some years ago Dr. James B. Herrick, the first to comment on this relationship between angina and anemia,[4] admitted in a private conversation in all the cases of this type he had seen, autopsy examination always revealed coronary sclerosis. He had never seen a classic instance of angina due to anemia in which the coronary arteries were normal.

A similar relationship obtains in the combination of hyperthyroidism and angina. When both conditions coexist, angina may be ameliorated or practically disappear when the thyrotoxicosis is cured, but careful follow-up studies and eventual pathologic examination will almost invariably show that the anginal state merely remained latent, or that the coronary arteries were structurally diseased. We have found in the literature only one example of this condition which on postmortem examination showed normal coronary arteries.[10]

We wish to report two instances of definite angina pectoris examined post mortem in which the coronary arteries were normal. One was a case of severe

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From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School, Boston, Massachusetts. These studies were aided in part by a grant from the United States Public Health Service (No. H-445(C2)).

refractory anemia in a young woman, the other a case of extensive amyloid involvement of the heart muscle. In both instances the diagnosis of angina was made by one of us (S. A. L.) after eliciting a clear-cut history of anginal pain, this being the only method of making the diagnosis of angina.

Case Reports

Case 1. A 30 year old Portuguese female was seen for the first time at the Peter Bent Brigham Hospital on December 14, 1946, when she was admitted with marked anemia and a history of intermittent left lower abdominal pain of one year's duration. Three months prior to admission her menses had become irregular, and the onset of metrorrhagia and menorrhagia was noted. Two months later she had epistaxis and bleeding from her oral mucosa, where purpuric spots were noted. During the week prior to admission she had a gradual increase in the severity of her abdominal pain.

The significant physical findings at this admission were tenderness in the left lower quadrant and slight hepatomegaly.

It was concluded that the manifestations of leukopenia, lymphocytosis, macrocytosis, low reticulocyte count, thrombocytopenia and normal bone marrow iron indicated a refractory anemia of unknown etiology. The patient was given a therapeutic trial of folic acid, without success. Attempts were made at sterilization by radiation therapy because of continuing vaginal bleeding, but she developed a severe leukopenia and the radiation treatments were discontinued. Multiple transfusions of both fresh and banked blood were given as the only means of maintaining her hematocrit at a level higher than 14. Whenever her hematocrit fell to a level of 10 or 12 she experienced definite anginal pain. These symptoms appeared following either exertion or smoking a cigarette. When the hematocrit level had been restored to approximately 18, she was discharged from the hospital (February 28, 1947), to be followed in the out-patient Hematology Clinic.

She reëntered the hospital on March 13, 1947, with complaints of extreme exertional dyspnea, palpitation and progressive ankle edema, and was discharged two days later. She had noted no oral, nasal, vaginal or gastrointestinal bleeding during the interval since her discharge, but ecchymotic spots and purpuric lesions continued to appear. Because her hematocrit level had again fallen to 12, she was re-admitted for further transfusion therapy. Physical examination on this admission differed from her initial examination only in that a harsh, grade 3 systolic blowing murmur was heard over the mitral area. During the two days of hospitalization she received 1,300 c.c. of fresh whole blood, after which a decrease in dyspnea was noted.

On March 28 she was again admitted to the hospital, for one day, for further transfusions as a prophylaxis to prevent recurrences of the anginal pain she had experienced previously whenever her hematocrit fell to low levels. She had midsternal pressure without radiation, which she would notice while walking; and which forced her to stop for several minutes until it subsided. This pain never came at rest, it was present particularly when her hematocrit level was low, and it seemed to disappear after she received transfusions. She was given 1,000 c.c. of blood and the hematocrit rose to 24.

Four months after her initial admission she was admitted for the fourth and final time, with the chief complaint of a sore throat of one week's duration. Marked cervical adenopathy and bilateral enlarged hemorrhagic tonsils were present. The heart showed the same systolic murmur. The electrocardiogram showed only minor T wave changes (figure 1). She was placed on intravenous and intramuscular antibiotic therapy for 17 days while her temperature ranged between 101 and 105° F., after which period it fell slowly toward normal. A total of 15 transfusions was administered to combat the extremely refractory anemia. Despite all therapeutic efforts,

the patient's hematocrit fell below 10. On the twentieth hospital day, while in a semicomatose state, the patient's respirations became gasping and she died.

Autopsy Findings: Postmortem examination revealed a generalized petechial extravasation of blood throughout all organs. A serosanguineous pericardial effusion of 650 c.c. was found. The heart weighed 400 gm. No valvular abnormality or vegetation was found. The coronary arteries were yellow-white throughout and showed no atheromatous plaque, no calcification and no diminution of caliber. The coronary veins were not remarkable. The aorta was normally elastic and showed only a few discrete, noncalcified, raised, yellow atheromatous plaques in its distal portion.

Case 2. A 61 year old Italian-born laborer was first admitted to the Peter Bent Brigham Hospital on February 21, 1941, with complaints of frequent attacks of substernal pain and shortness of breath which had been noted for six months, and edema of the legs and scrotum which had been present for four weeks. He had been well all his life until approximately six months before admission, when he first noted dizziness and "black-and-blue spots" around his eyes. Soon thereafter he began to experience occasional attacks of transitory substernal pain, accompanied by shortness of breath and dizziness. The pain was squeezing and gripping in nature and frequently radiated to the right upper quadrant of the abdomen and into the right

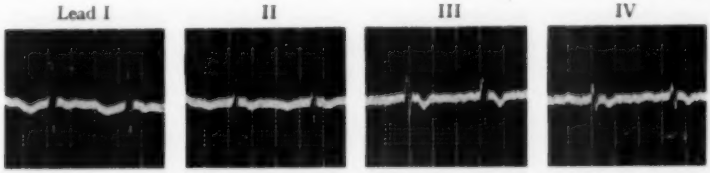

FIG. 1. Electrocardiogram, taken April 9, 1947, shows nonspecific lowering of T waves.

shoulder. It never radiated to the back, down the arms or into the neck, chin or jaw. The pain at first occurred two to four times daily and only while walking. It would cause the patient to stop walking, but after a rest of 15 to 20 seconds he could resume his way.

During the six months just prior to admission the attacks increased in frequency, occurring as often as 12 to 14 times daily. He never experienced pain at rest. The distress was notably aggravated on cold days. Four weeks before admission he first noted edema of his legs, particularly his ankles and calves, and a week later his scrotum began to swell. The edema gradually increased up to the time of admission to the hospital. Five days before admission he had two attacks of paroxysmal nocturnal dyspnea, but without associated cyanosis. The shortness of breath awakened the patient from a sound sleep on these two occasions and was accompanied by a substernal gripping pain. About this same time he also first noted a large, painless lump in his left axilla, which, however, did not cause limitation of motion of the arm. He also noted large purpuric areas on the inner surface of the left arm, the left side of the chest wall and on the dorsum of the left hand. The axillary mass and ecchymotic areas had persisted and were seen on physical examination at the hospital. Despite a good appetite, he had lost 21 pounds in weight during the six preceding months. The system review and past history were noncontributory.

Physical examination on admission revealed adenopathy involving the cervical, axillary and supraclavicular glands. Hepatomegaly, splenomegaly and marked edema of scrotum and ankles were present. Purpuric areas were observed over the hand, arm and chest wall on the left side. Right hydrothorax was detected. The blood

pressure was 118/82 mm. of Hg. The heart showed no abnormal sounds. An electrocardiogram taken February 27 showed first degree A–V block (P–R interval, 0.24 sec.), and the QRS complexes were of low amplitude, with slight inversion of T waves in Leads I and CF_4 (figure 2). A roentgenogram of the chest on admission showed marked cardiac enlargement, some fluid in the right pleural cavity and a questionable area of consolidation at the right base.

During the nine days in the hospital he complained of mild shortness of breath and slight orthopnea. The edema was believed to be the result of cardiac failure. A biopsy of a left axillary node showed merely an old hematoma, but one of a left inguinal gland showed amyloidosis. Significant diminution of the peripheral edema followed bed-rest. However, he was given 1.3 gm. of digitalis during the last three days of hospitalization. Sudden weakness, lightheadedness and syncope occurred about 4 p.m. on the eighth day. Although his pulse was found to be only 48, his blood pressure remained at 110/70 mm. of Hg. Four hours later he vomited 200 c.c. of coffee-ground material. At about 1 a.m. on the morning of his ninth hospital day he complained of severe epigastric pain radiating around the left costal margin to the back. He became very apprehensive and restless. His blood pressure at this time was found to be 72/50 mm. of Hg. Following a hypodermic injection of mor-

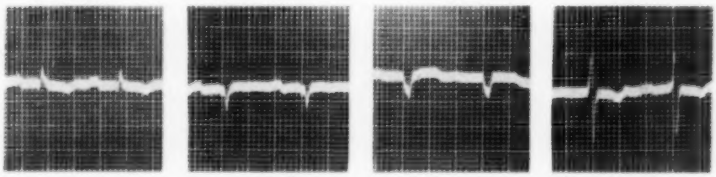

FIG. 2. Electrocardiogram, taken February 27, 1941, shows first degree heart block (P–R = 0.24), low QRS waves and slight inversion of T_1 and T_{CF_4}.

phine, the patient went to sleep with no change in vital signs. He died suddenly and quietly at 4:40 a.m.

Autopsy Findings: Postmortem examination revealed generalized amyloidosis, cardiac hypertrophy and dilatation, hydrothorax, pulmonary edema and purpura. The heart weighed 670 gm. No valvular abnormality or vegetation was observed. The myocardium was abnormally firm in consistency and texture, and the cut surface appeared rather pale gray in color. The myocardium showed extensive and generalized infiltration with amyloid. There was a considerable decrease in the amount of muscle fibers due to compression and atrophy. No mural thrombi or evidence of infarction or scarring was seen. The coronary arteries were not markedly tortuous and were of normal caliber and consistency. No evidence of occlusion, no calcification and no thrombi were found along the course of the coronary arteries. The aorta showed good elasticity, and the aortic sinuses and the coronary ostia appeared normal.

COMMENT

It is well known that angina pectoris is rare in the absence of coronary disease. There is, however, a small but not insignificant group of cases suffering from other types of heart disease, i.e., aortic and mitral valvular disease, or hypertensive heart disease in which angina has been present and the coronary arteries have been found to be normal. Much rarer still is the combination of angina with

normal coronary arteries and anemia or amyloid disease of the myocardium. Although in the medical literature there are isolated, well-documented cases of anemia with angina in the absence of coronary disease, we have found no such case of amyloid disease.

SUMMARY

Two cases of definite angina pectoris are reported in which the coronary arteries post mortem were found to be normal. The first was a 30 year old woman with refractory anemia, the second a 61 year old man with diffuse amyloid disease involving the heart muscle.

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TETRALOGY OF FALLOT: REPORT OF A CASE THAT SURVIVED TO HIS FIFTY-SEVENTH YEAR AND DIED FOLLOWING SURGICAL RELIEF OF GALL-STONE ILEUS *

By SAM I. MILLER, M.D., *Houston, Texas*

PATIENTS with Tetralogy of Fallot rarely live beyond the third decade, and only seven patients who survived beyond this age have been reported. The mean age of survival in Maude Abbott's series was 12 years.[1] The reported patients [2, 3, 4, 5, 6, 7] lived from 41 to 60 years of age.

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The rarity of survival of such patients to the sixth decade of life warrants recording; for this reason a patient who survived to 56 years of age and died from another cause is reported.

Case Report

A 56 year old white man was first seen October 27, 1948, for cramping periumbilical pain of 36 hours' duration. He had experienced periodic attacks of abdominal pain for years. During the last attack he was unable to retain food or water for 36 hours and had passed no feces or gas by rectum. He was said to have been a blue baby; the diagnosis of Tetralogy of Fallot had been made many years before, and he had been told repeatedly that he could not live more than six months longer. He grew and developed normally. Any sudden exertion was always accompanied by shortness of breath, but he was able to do a good bit of work at a slow rate of speed. He had been an automobile race driver and had piloted aeroplanes. During the last years of his life he had been night watchman for a large department store, and had climbed as many as seven flights of stairs during the night.

The family history was noncontributory. The patient was unmarried. The past history was negative except for pneumonia at the age of two years and the history of repeated bouts of abdominal pain. Rheumatic fever and venereal disease were denied by name and symptom.

He appeared acutely ill and cyanotic. The conjunctivae were extremely congested but were not icteric. The neck veins were not distended but the carotid artery pulsations were prominent. The fingers and toes were moderately clubbed. The arterial pressures were 122 mm. Hg systolic and 85 mm. diastolic. The cardiac rate was 90 beats per minute. The anteroposterior diameter of the chest was slightly increased, with moderate heaving of the lower sternal area. A systolic thrill was palpable in the fourth interspace to the left of the sternum. The left border was about 1 cm. outside the midclavicular line. A very loud grade V systolic murmur was heard over the entire precordium, loudest along the left sternal border; it was transmitted to the neck vessels and to the back. The first sound at the apex was very loud and the aortic second sound was sharp, but the pulmonic sound was very soft. Diastolic murmurs were not heard. The lungs were clear on auscultation and percussion. The abdomen was moderately distended, without peristaltic sounds except when a cramp-like pain appeared. Tenderness was noted in the right lower quadrant, with questionable rebound tenderness, but rigidity of the abdominal muscles was not demonstrated. Varicosities of both legs were present, with slight swelling of the right ankle. Numerous pigmented scars were present over both shins.

A diagnosis of Tetralogy of Fallot and intestinal obstruction was made, and the patient was admitted to Hermann Hospital. A distended loop of small intestine, several small calcifications in the gall-bladder region and a circular area of increased density 3 cm. in diameter just above the right iliac crest were noted in a roentgenogram of the abdomen (figure 1).

Specific gravity of the urine was 1.038, with 3 plus albumin and no sugar. Acetone and diacetic acid were reported to be present. Following centrifugation, 1 to 2 white blood cells and 2 to 3 red blood cells were present in each high power field. The erythrocytes numbered 6,280,000 per cu. mm. with 9,900 leukocytes. The hemoglobin was 22.5 gm. per 100 c.c.

A Miller-Abbott tube was inserted into the stomach, and glucose and saline were administered very slowly intravenously. Procaine penicillin, 300,000 units, was administered intramuscularly every 12 hours. The next morning the patient was not improved. The Miller-Abbott tube had not passed the pylorus, and the abdominal

distention had increased. The leukocyte count had risen to 13,500, and the blood chlorides were 330 mg./100 c.c. The icteric index was 8 units.

An exploratory laparotomy under cyclopropane-ether anesthesia was done by Dr. Emile Zax, and a large gall-stone, 3 cm. in diameter, was found to be lodged a

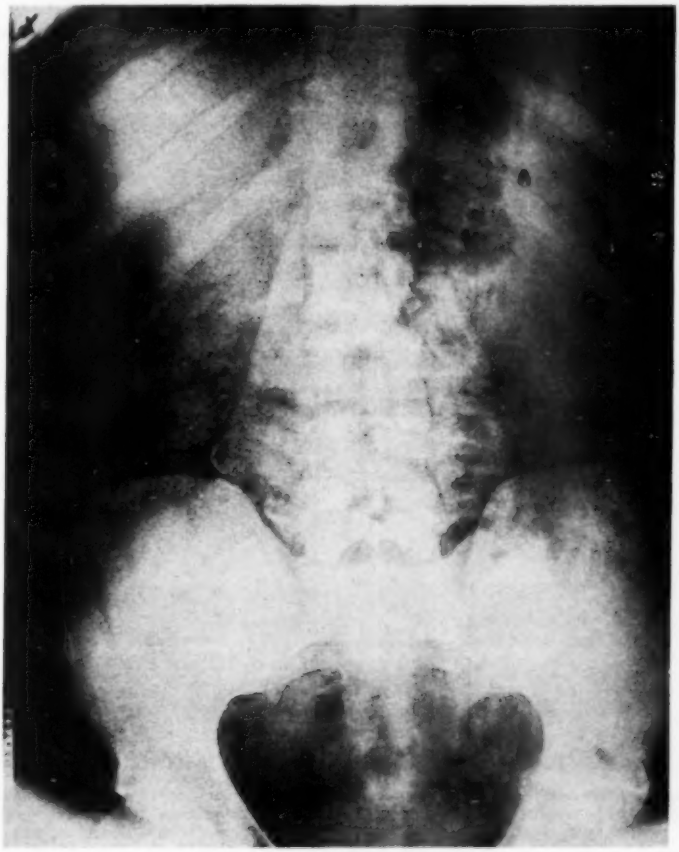

FIG. 1. The arrow points to the gall-stone obstructing the ileum. Dilated loops of small intestine are seen at A.

few inches above the ileocecal valve. The stone was removed, and the patient left the operating room in fair condition.

He improved with the usual postoperative therapy. The arterial pressures were 104 mm. Hg systolic and 66 mm. diastolic on the fourth postoperative day when he suddenly developed auricular fibrillation with a ventricular rate of 190 beats per minute and a pulse deficit of about 50 per minute. An electrocardiogram confirmed

the diagnosis, and 1.0 mg. of digitoxin was administered intravenously. The ventricular rate continued elevated, and at 2 p.m. it was still 150 beats per minute. Digitoxin, 0.4 mg., was administered intravenously with 50 mg. of heparin. The arterial pressures were maintained at 106/60. An hour and a quarter later he suddenly became unresponsive: a right-sided hemiplegia had developed. His blood clotting time (Lee-White) was three minutes. Heparin therapy was discontinued. Digitoxin, 0.2 mg., was again given an hour and a quarter later; three hours later he became restless, the respiration increased, and moist râles were noted in both lung bases. The ventricular rate continued at 130 beats per minute, with a pulse deficit of 20 per minute.

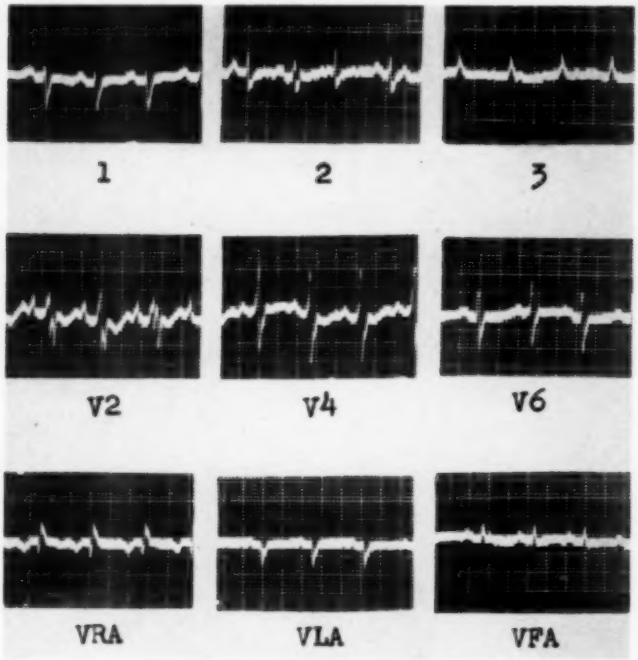

FIG. 2. Electrocardiogram made on November 2, 1948, showing sinus tachycardia and marked right axis.

One hour later he went into severe pulmonary edema. Tourniquets were applied to all four extremities; morphine, gr. 0.25, aminophylline, gr. 3.75 and Mercuhydrin, 2 c.c., were administered intravenously, and 300 c.c. of blood were removed by venesection.

The pulmonary edema gradually improved, but the patient responded only to the most extreme stimuli, and presented the findings of a right-sided hemiplegia. The auricular fibrillation persisted for two days and stopped with a sinus rhythm and a ventricular rate of 110 beats per minute (figure 2). The body temperature fluctuated between 102 and 103° F. (by axilla). At 2:30 a.m. on November 3, the seventh postoperative day, a large quantity of foul material was passed through the lower end

of the abdominal incision. He became progressively weaker, auricular fibrillation returned, and at 7:10 a.m. he died.

The autopsy was performed by Dr. Violet Keiller, and the heart was dissected by Dr. Luke Able. The body was that of a poorly nourished middle aged white man. The abdominal incision had necrotic wound edges with complete wound dehiscence.

The pericardial cavity contained approximately 500 c.c. of fresh blood, and a perforation was noted through the visceral pericardium from the left atrium at its juncture with the right superior pulmonary vein. The pericardium was not thickened, and adhesions were not present.

FIG. 3. The heart is shown with the right ventricle opened. The arrow points to the septal defect through which the probe within the cavity of the left ventricle is visible. R. V. denotes the cut wall of the right ventricle. The tricuspid valve is labeled.

The heart (figures 3, 4 and 5) weighed 425 gm. The right ventricle was situated somewhat anteriorly, and the interventricular septum was situated midway between the sagittal and the coronal plane. The aorta ascended toward the right of the vertebral column, and the descending aorta was located to the right of the spinal column until it passed through the diaphragm. The innominate artery, the right common carotid artery and the right subclavian artery arose from the aortic arch in the sagittal plane, with the innominate artery located anteriorly and curving to the left, and branching to form a left common carotid artery and a left subclavian artery. The

left recurrent laryngeal nerve coursed inferiorly to the left subclavian artery. The right atrium was exceedingly large, almost encircling the entire heart above the atrioventricular valve ring. The tips of each auricular appendage were separated anteriorly only by a distance of 5 cm. The left atrium was extremely small. The foramen ovale was closed. The right pulmonary veins entered the left atrium on the right side posterior to the origin of the aorta. Just proximal to the juncture of the right superior pulmonary vein and the left atrium there was an irregularly shaped rent in the wall of the vein, 0.3 cm. in diameter, from which the blood in the peri-

FIG. 4. The numeral 1 lies within the opened pulmonary artery. The arrow points to the tiny aperture which is the pulmonary valve. The numeral 2 denotes the opened arch of the aorta.

cardial cavity had issued. No signs of inflammatory reaction were noted about this tear. The left pulmonary veins entered the atrium on the left side also posterior to the aorta. When the heart was opened the aorta arose mostly from the right ventricle and overrode a defect in the upper end of the interventricular septum, which measured 2 cm. in diameter. The pulmonary conus, which arose from the right ventricle, was

FIG. 5. The forceps is placed under two large bronchial arteries, either one of which in life probably transmitted as much blood as the stenosed pulmonary valve.

extremely narrow, and the pulmonary valve was a solid thickened fibrous plate of valvular tissue in the form of a ring without cusps but with an irregularly shaped central aperture measuring 0.5 cm. in diameter (figure 4). The conus terminated in a small pulmonary artery which branched in the usual manner. There was no trace of the ductus arteriosus. The wall of the right ventricle measured 1.8 cm. in

thickness and was equal in thickness to the wall of the left ventricle. There was moderate thickening of the aortic and tricuspid valves, but the mitral valve was normal. The orifices and distribution of the coronary arteries were normal.

The aorta showed numerous large and small atheromatous plaques in its wall. The coronary orifices were normal in size, although atheroma was present. The coronary vessels showed minimal sclerosis. Generalized arteriosclerosis of moderate severity was present throughout the body. Large bronchial arteries were noted posteriorly at the carina of the trachea, and while they were very large their distribution was normal (figure 5). From their caliber it seemed likely that each one was able to carry as much blood as the stenotic pulmonary artery, and that they accounted for a large proportion of the pulmonary arterial blood flow during life. The pulmonary artery and its branches were free of arteriosclerosis and were normal in distribution.

Very dense adhesions were present over the entire lateral surface of the right lung, and the lower lobe was densely adherent to the diaphragm. Similar adhesions were found over the left lower lobe. Both lungs were congested and, on section, portions showed small areas of gross hemorrhage. No consolidation was present.

The peritoneal cavity contained approximately 500 c.c. of sanguinopurulent fluid. The cecum was dusky red, and the ileotomy incision was sealed with fibrin and surrounded by fibrinous adhesions from the omentum. The ileum was dusky but not gangrenous about the ileotomy.

The gall-bladder was adherent to the first portion of the duodenum by very wide and thick adhesions. A fistula 2 cm. in diameter was present between a separate fibrous compartment of the gall-bladder and the lumen of the first portion of the duodenum. The first part of the jejunum was greatly distended from no apparent cause.

In the left occipital lobe of the cerebrum there was an area of fresh hemorrhage measuring 3 cm. in anteroposterior diameter by 1 cm. in depth by 2 cm. in coronal plane. In the left side of the cerebellum, on its ventral surface, there was an old area of necrosis measuring 4 cm. by 1.5 cm. by 0.5 cm. On sectioning, after formalin fixation, four other areas of necrosis were located in the left occiput, right caudate nucleus, substantia nigra and the right frontal lobe. Old blood pigment was found in these areas, indicating older small hemorrhages.

Microscopic examination of the lungs showed marked thickening and fibrosis of the pleura, with much anthracotic pigment in the fibrous tissue and many collections of lymphocytes. The outer layers of pleura, where adhesions had been separated, showed one or two large veins and many small venous channels. No arterioles were demonstrated in this tissue. Most of the vessels noted were small venous channels, engorged with blood. A small patch of bronchopneumonia was present in one section. The site of rupture in the pulmonary vein had been found by probing, and this method of demonstration had been used frequently before sections were cut. The effect of this was to render the interpretation somewhat difficult. The pericardial fat here was vascular but otherwise normal. The wall of the pulmonary vein was thin. In the center of one section there was a small amount of hemorrhage marking the site of rupture, although the actual point of rupture was not demonstrated. There was a very slight diffuse inflammatory reaction present. Microscopic examination of the other organs confirmed the gross findings.

Comment

This patient presented all of the classic findings of Tetralogy of Fallot, with the addition of a rather rare surgical complication: gall-stone ileus. The reason for the long survival of this man, despite severe pulmonary artery stenosis, can

be conjectured. Bing et al.[8] have shown by measurements of the pulmonary capillary flow that, in older patients with Tetralogy of Fallot (the oldest in their series was 26 years), the pulmonary capillary flow per minute exceeds the pulmonary artery flow by as much as 1,132 c.c. per square meter of body surface per minute. Obviously this extra flow must come from collateral circulation which might be formed via the bronchial arteries, vascular pleural adhesions, patent ductus arteriosus or aberrant vessels. At surgery, the oldest patient in Bing's series, who also had the largest difference in pulmonary artery and capillary flow, was found to have a pleural cavity obliterated by adhesions through which numerous collaterals from the intercostal and mammary arteries passed to the lungs.

Our patient not only had numerous vascular pleural adhesions but his bronchial arteries were capable of carrying a much larger volume of blood than normal. It is possible that the pneumonia he survived at the age of two was the means of providing adhesions which, when vascularized, added the additional pulmonary circulation that allowed him to live into his fifty-seventh year.

The relation of the gall-stone formation to the polycythemia associated with Tetralogy of Fallot is unknown, but it is interesting that Middleton and Ritchie's [6] patient had a cholecystectomy at 25 years of age for gall-stone and finally died in heart failure at 45. Gall-stone ileus is a rare cause of obstruction occurring only 18 times in the records of The Mayo Clinic.[9] The combination of gall-stone ileus and Tetralogy of Fallot is indeed a medical curiosity.

Cerebral accidents are common in Tetralogy of Fallot, accounting for seven deaths out of 40 cases followed to exitus in Maude Abbott's series.[1] The effect of heparin on the cerebral hemorrhage could only have been adverse, but it was given in an attempt to prevent thrombosis when the rapid rhythm supervened. The rupture of the pulmonary vein with terminal tamponade is unique in our experience. Some lesion which we were unable to demonstrate may have weakened the wall of this vessel, or the tremendous increase in the intraluminal pressure due to heart failure may have ruptured an essentially normal vessel.

The failure of the ileotomy to close and the subsequent wound dehiscence were undoubtedly due to the poor condition of the patient after the hemiplegia and cardiac failure.

Summary

A case of Tetralogy of Fallot is reported who survived and led an active life into his fifty-seventh year. Death followed ileotomy for gall-stone ileus, which was complicated by auricular fibrillation, cerebral hemorrhage and terminal cardiac tamponade. Dilated bronchial arteries and vascular pleural adhesions probably furnished the additional pulmonary flow which allowed this patient to lead an active life for 56 years.

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EDITORIAL

ACTH, CORTISONE AND HYPERSENSITIVE DISEASE STATES

RECENT studies with ACTH and cortisone have demonstrated remarkable, albeit often transitory, effects of these hormones upon a large group of diseases of known hypersensitive etiology. These results have encouraged wider exploration of the therapeutic potentialities of the corticoids in diseases of obscure etiology where hypersensitive mechanisms have been suspected, but not proved. The beneficial effects of hormonal therapy in such widely separated entities as acquired hemolytic anemia,[1] sympathetic ophthalmia,[2] ulcerative colitis,[3] and experimental acute disseminated encephalomyelitis,[4] to name but a few, have aroused renewed interest in a search for common denominators. A brief survey of recent contributions to these problems will be attempted.

In the study of known hypersensitive syndromes as well as those of more mysterious etiology, the influence of adrenal cortical hormones on mineral and carbohydrate metabolism has been relegated to the position of undesirable side-effect. More interest is attached to their influence upon nitrogen metabolism, mesenchymal tissue, and immune phenomena. There is some evidence that the beneficial effect of hormonal therapy may be mediated through one or more of these pathways. By decreasing the synthesis of proteins from amino acids (anti-anabolic effect) ACTH and cortisone produce a negative nitrogen balance in the treated individual.[5] It has been suggested that this may be one of the contributing mechanisms in the reduction of antibody titer. It is of interest to note, in this connection, that the rate of disappearance of preformed antibody injected into the blood stream of treated and untreated animals was essentially the same.[6]

Animal and human experiments have conclusively demonstrated that the administration of ACTH and/or cortisone results in atrophy of the thymus, spleen and lymph nodes with, at least, a transient reduction in circulating lymphocytes.[7] This lymphocytolytic action is likewise believed to have an inhibiting effect upon the production of antibodies. The original observa-

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[7] Ingle, D. J.: The biologic properties of cortisone: a review, J. Clin. Endocrinology **10**: 1312, 1950.

tions of Dougherty, Chase and White [8] correlating lymphocytolysis with a rise in circulating antibody levels have not been confirmed. There is still some question, from the available data, regarding the exact effect of these hormones upon the level of circulating antibody. Wedgewood et al.[9] in experiments designed to study the effect of ACTH on the production of experimental nephritis by bovine serum gamma globulin failed to observe any significant difference in antibody levels in treated and untreated animals. Using more exact immunochemical technics, Bjørneboe et al.,[10] however, were able to demonstrate reduction in the amount of antibody produced in response to immunization by polyvalent pneumococci in animals treated with ACTH. Germuth and Ottinger [11] obtained essentially similar results with egg-albumin as the antigen.

Despite the volume of intensive investigation to date, the impression is gained from the literature that much additional information will be needed before the influence of ACTH and cortisone upon specific immune phenomena is clear. The previously cited data upon circulating antibody levels is a case in point. Studies have been made of such classical immune phenomena as the Arthus reaction. This necrotizing allergic tissue reaction is brought about, classically, by the repeated inoculation of antigen (horse serum) intradermally in the experimental animal (rabbit) until a point is reached where the reaction progresses to necrosis and sloughing. It is associated with demonstrable circulating antibody and is classified as a local anaphylactic reaction. Pathologically, it is characterized by vascular involvement with ultimate thrombosis. This is the so-called active Arthus reaction. By inoculating the experimental animal intradermally with antigen and intravenously with specific antibody a passive Arthus reaction may be produced. The Arthus reaction is by no means confined to the skin, but has also been produced experimentally in the gastric submucosa, kidney, liver, brain, joints, etc. It may be viewed as a prototype of certain allergic reactions in the human. Germuth and Ottinger [11] observed inhibition of the Arthus phenomenon in animals treated with ACTH. Fischel, on the other hand, using the passive Arthus reaction technic observed no inhibition by hormonal treatment.[12] The effect in the active Arthus reaction may have been due to diminished antibody formation, since it has been shown that the degree of reaction is dependent upon antibody titer.

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In studies on other immune mechanisms Fischel [12] noted no inhibition of the systemic anaphylactic reaction or of the tuberculin reaction. Grob et al.[13] in human allergic subjects noted a prompt decrease in the reactivity of allergic tissue (bronchial tree in asthmatics) to specific allergen after treatment with ACTH. The allergic tissue response to histamine and mecholyl was, however, unaffected. The mechanism of the beneficial effect, with regard to the allergen, was not settled by these experiments, but, in a negative way, it was shown that this unresponsiveness was not mediated through lack of response to a cholinergic substance (mecholyl) or through altered reactivity to histamine.

The well-documented effect of ACTH and cortisone upon the so-called collagen diseases has resulted in the focusing of considerable interest upon the reaction of mesenchymal tissue to these hormones. Sprague [14] has summarized these effects as follows: inhibition of reactivity to a variety of injurious agents, interference with the formation of granulation tissue and the infiltration of lymphocytes, inhibition of fibroblastic proliferation and later scar formation.

To summarize then, an examination of the data reported in the recent literature suggests that the beneficial effects of ACTH and cortisone upon hypersensitive disease are in part due to inhibition of the formation of antibody as well as diminished reactivity of the end organ particularly in the case of mesenchymal tissue. Mechanisms of action are imperfectly understood at present. That the action is at some fundamental biochemical level is suggested by the wide variety of animal species response as well as the variety of injurious reagents blocked. In this sense, at least, the action of these hormones must be regarded as non-specific or pharmacodynamic in character.

Although the evidence for including certain of the collagen diseases in the allergic group is quite convincing—notably periarteritis nodosa and serum sickness—data to support a similar conclusion in others are still lacking.[15] Suggestive evidence, however, continues to accumulate. Of particular interest is the increasingly frequent discovery of the association of acquired hemolytic anemia and acute disseminated lupus erythematosus.[16] The former disease can conclusively be shown to be due to an auto-antibody with affinity for the patient's own erythrocytes. The characteristics of the antibody have been extensively studied and the favorable response to steroid hormone therapy well documented. A high incidence of female involvement, resembling in this respect L.E.D., has also been recently noted. Rantz

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et al.[17] have reported recently that a characteristic of the rheumatic subject and others suffering from diseases in which inappropriate immune responses may play a rôle, is their "hyperreactivity" to all kinds of antigenic stimuli. The study of patients with L.E.D. or acquired hemolytic anemia tends to bear out this observation. The simultaneous, although incomplete, response to therapy of the patient with both diseases is also of interest.

Evans et al.[18] have recently reported the concomitant finding of acquired hemolytic anemia and essential thrombocytopenic purpura in a number of patients and have suggested a common etiological mechanism, i.e. auto-antibody formation. This suggestion has received additional support from the studies of Harrington et al.[19] in 10 patients with essential thrombocytopenic purpura. In 8 of the 10 a circulating factor in the globulin fraction of the patient's plasma was found to be capable of producing a sharp drop in the platelet count of normal recipients and the appearance of purpuric manifestations. The factor persisted in some patients after splenectomy. The influence of ACTH was studied in two patients. In one no effect was observed, but in the other the coincident rise in platelet count under therapy was associated with failure of the factor to produce thrombopenia in a normal recipient. Bethell et al.[20] have recently reported the favorable response of 10 patients with essential thrombocytopenic purpura to cortisone or ACTH. The essayist has likewise had a similar experience with six patients. Studies of these cases are still too incomplete to permit detailed evaluation of the results.

Another entity which seems to bridge the gap between hematologic disease of hypersensitive etiology and the collagen group is thrombotic thrombocytopenic purpura. This entity, first described by Moschcowitz[21] in 1925, is characterized by hemolytic anemia, thrombocytopenic purpura and arteriolar occlusions, particularly in the brain, leading to focal neurologic signs and mental aberrations. Several authors have recently called attention to the similarity of the vascular lesions of this disease and those of the collagen-vascular group.[22, 23, 24] A partial response in one patient to ACTH has been reported.

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Over a period of years Wolf and coworkers have studied the problem of experimental acute disseminated encephalomyelitis produced in animals by repeated injections of brain emulsions. A high percentage of positive "takes" occurs when the antigen is mixed with an adjuvant according to the Freund technic.[25] The adjuvant consists of killed tubercle bacilli, aquaphor, a lanolin-like substance, and paraffin oil. One or two injections of the mixture are followed within 25 to 33 days by the specific disease. The lesions of this experimental disease have been compared to human multiple sclerosis. Recently Kabat et al.[4] have reported inhibition of the disease in monkeys by the use of cortone prior to injection of brain antigen and for 10 weeks thereafter. At the same time the site of inoculation of the brain tissue and adjuvant showed marked inhibition of the granulomatous response. Suggestive early results in humans with multiple sclerosis after treatment with cortisone and ACTH have recently been reported by Glaser et al.[26] Because of the known tendency of this disease to remit spontaneously, extreme caution in evaluation of the results is essential. McLean [27] has noted "dramatic" improvement in two patients with multiple sclerosis who developed retrobulbar neuritis.

A considerable body of data has accumulated in ophthalmological literature regarding the possible hypersensitive etiology of sympathetic ophthalmia. Collins [28] has recently presented impressive evidence supporting an auto-immune etiology of this distressing disease. Recent reports of the successful management of this disease have been quite encouraging.[29]

Although the beneficial effects of ACTH and cortisone in the widely disparate group of diseases mentioned above may be due to a non-specific inhibition of tissue reactivity, the possibility that they are the result of interference with the noxious effects of antigen-antibody reactions cannot be completely excluded. Failure to demonstrate the immune mechanisms may be the fault of inadequate technic. The partially encouraging therapeutic results should prove a potent stimulus to further investigation.

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REVIEWS

Die neuzeitlichen Brustwand- und Extremitäten-Ableitungen in der Praxis. By HERBERT REINDELL and HELMUTH KLEPZIG. 179 pages; 17.5 × 25 cm. Georg Thieme Verlag, Stuttgart; agents for U. S. A.: Grune & Stratton, Inc., New York. 1951. Price, Ganzleinen DM 22.50.

This monograph discusses the theories and clinical value of chest and extremity leads. The material is based essentially upon the contributions of American investigators during the past 20 years.

An adequate presentation of the historical development and concepts of the central terminal of Wilson is given. The discussion of the theories and the underlying basic physical laws is very clear, without resort to the trigonometric form of presentation.

After a well illustrated chapter of variations of the individual waves, a discussion of the "unipolar" chest and extremity leads in the normal adult, infant and child is given. This is followed by an excellent chapter on their value for the diagnosis of myocardial infarction. The diagnostic features of chamber hypertrophy, conduction defects and bundle branch block lesions are equally well presented.

One might differ with some of the explanations given for the configuration of hypertrophy and other minor topics. Since no idea of these problems can be stated with certainty, the authors are certainly entitled to theirs, particularly when presented as well as they have done. The references are extensive; the numerous illustrations are of excellent quality. Although based mainly upon work done by other investigators, the authors have written an excellent book on chest and extremity lead electrocardiography. The mode of presentation is lucid, simple and still not devoid of theoretical explanations. This book can be recommended for practitioners, internists and cardiologists familiar with the German language.

A. G.

Chest X-ray Diagnosis. By MAX RITVO, M.D., Assistant Professor of Radiology, Harvard Medical School; Roentgenologist-in-chief and Director, Department of Radiology, Boston City Hospital; Associate Radiologist, Beth Israel Hospital, Boston, Massachusetts; Radiologist, Jewish Memorial Hospital, Jewish Tuberculosis Sanitorium of New England, Revere Memorial Hospital and Hudson Hospital. 558 pages; 18 × 26.5 cm. Lea & Febiger, Philadelphia, Pa. 1951. Price, $15.00.

This is a well-organized and very complete text relative to the roentgen manifestations of diseases and abnormalities of the chest. The book is presented in 10 general sections: The Lungs, Mediastinum, Diaphragm, Pleura, Bony Thorax and Chest Wall, Soft Tissues of the Neck, Heart and Great Vessels, Aorta, Pulmonary Artery and the Pericardium. There are many illustrations, all of which are well reproduced. There are only a few diseases or abnormalities that are not well illustrated. Discussion, differential diagnosis and, in many instances, clinical aspects are dealt with at considerable length. Numerous bibliographies as to source of material and additional reading follow the discussion of each condition.

Under the section devoted to methods of examination of the lungs the author describes the technic of bronchography and emphasizes the importance of visualizing all of the various pulmonary segments. However, in only a few of the illustrations where bronchography was done is there adequate demonstration of the segments.

Complete visualization of the broncho-pulmonary segments is imperative both from a diagnostic and therapeutic approach to many chest lesions.

In reading this book one cannot but be impressed by the wide experience of the author in roentgenology of the chest. Radiologists, internists, chest physicians, as well as students, will find it a very informative and well written book.

C. N. D.

Textbook of Physiology and Biochemistry. By GEORGE H. BELL, B.Sc., M.D. (Glasg.), F.R.F.P.S.G., F.R.S.E., J. NORMAN DAVIDSON, M.D., D.Sc. (Edin.), F.R.F.P.S.G., F.R.I.C., F.R.S.E., and HAROLD SCARBOROUGH, M.B., Ph.D. (Edin.), F.R.C.P.E. 918 pages; 17 × 24.5 cm. The Williams and Wilkins Company, Baltimore, Maryland. 1950. Price, $9.00.

This book, written by British professors of physiology, biochemistry, and medicine, respectively, constitutes an excellent synthesis and integration of biochemistry, neurophysiology and physiology. One finds the fundamentals of these basic sciences clearly stated and closely interwoven with medical theory and practice. It tends to demonstrate the vanishing borders between these subjects. The authors state that their objective was to write not only an introductory book on physiology and biological chemistry for students of medicine and the allied sciences, but one which would contain sufficient "material of an applied and clinical nature to emphasize the importance of physiological knowledge in clinical medicine." "Our aim has been to treat these two subjects as one and to indicate, wherever possible, their relevance to clinical problems." In a foreword, Dr. R. C. Garry of the University of Glasgow aptly writes, "This book is designed to lay a sure foundation for the medical undergraduate. . . . The medical student neglects his study of Physiology and Biochemistry at the peril of his future patients."

It is this reviewer's opinion that these objectives have been well attained. In addition, the book should prove extremely valuable both to the young doctor reviewing these preclinical subjects for his various board examinations, and to the physician who wishes to renew his knowledge of subjects which are developing at an ever faster rate.

The book contains approximately 900 pages, equally divided among biochemistry, physiology and neurophysiology. In general, the individual topics included in the 56 chapters are those usually found in books on these subjects. The authors state that they have not tried to include the latest work but rather that which is based on a firm foundation and "in trying to effect a judicious selection, we realize that we have laid ourselves open to the accusation of failing to be up to date." While the reviewer feels that, as a whole, the subject matter is well selected and up to date, the reader is justified in expecting a more adequate treatment of such important and well-established topics as sulfonamide chemistry, antibiotics and metabolic antagonism. Because of the rapid developments in many of the subjects covered in this text, the authors should be warned that revisions must be frequent if the volume is to retain its maximum usefulness.

Illustrations, photographs, figures, drawings, diagrams, tables, etc., are unusually abundant and are well selected to clarify the text. These aids should be most helpful, both to the teacher in the preparation of his lectures, and to the student or doctor seeking a clearer understanding of these various topics. The chapters on vitamins, respiratory functions of blood, intermediary metabolism and hormones were particularly interesting and helpful to this reviewer. At the end of most chapters, the reader is referred to a number of appropriate reviews, monographs, research papers, etc., on the particular material covered therein. The type, paper and format are

quite satisfactory and, as is characteristic of most British scientific writings, the authors' literary standards are high, the style of writing pleasing and the content is readily understood. The authors and publishers merit the appreciation of all students, doctors, and teachers in the biological sciences.

E. G. S.

Klinische Physiologie und Pathologie. By FERDINAND HOFF. 782 pages; 17.5 × 25 cm. Georg Thieme Verlag, Stuttgart; agents for U. S. A.: Grune & Stratton, Inc., New York. 1950. Price, Ganzleinen DM 39.—.

The author has started with the premise that the progress of medicine requires a scientific understanding of the processes of disease rather than simply descriptions of signs and symptoms and empirical therapeutic measures. Grouped under the various systems, he has considered a long list of diseases from the standpoint of the abnormal tissue structure and physiological processes involved. The book is written from the standpoint of the clinician, but might be considered as an expanded form of a textbook of medicine with deletion of most of the diagnostic and therapeutic considerations, except insofar as these shed light on the basic nature and pathogenesis of the diseases. The need for such attempts to coördinate clinical medicine with the progress of the basic medical sciences is evident, and several such volumes in English have appeared in recent years.

The author has undertaken to cover the whole field of medicine himself rather than to distribute the topics to individuals who specialize in them. This may be justified by the fact that he has made original contributions in an unusual number of these fields. Some objection may be made to the tendency to assertions which are apparently to be accepted on the authority of the author alone. Some of these are thought-provoking, and the reader would like to inquire into their background. However, these items usually do not have specific journal references, most of the bibliography being textbooks and other treatises.

In general, the volume is successful in emphasizing the most essential principles of the pathogenesis of various diseases. Inevitably, the treatment must seem superficial to those who are concerned with research in the subjects, but the author has made a satisfactory compromise in selecting major points to be presented in sufficient brevity to comprise a volume of reasonable size and technicality.

The volume is flavored with much of the personal interest of the author in the relation of the whole organism to its parts and in the psychosomatic philosophy. The language is clear, and a number of very good original illustrations are presented.

G. E. G.

Cardiac Pain. By SEYMOUR H. RINZLER, M.D., F.A.C.P., Beth Israel Hospital and New York University College of Medicine, New York. 139 pages. Charles C Thomas, Springfield, Ill. 1951. Price, $3.75.

This small volume discusses the history, anatomy, pathogenesis and medical and surgical therapy of cardiac pain. Approximately 77 pages are devoted to text, 9 to illustrations, 24 to references and 27 to the index. About 11 pages in all are devoted to local block therapy for the relief of cardiac pain.

The author states that, in trying to distinguish somatic from cardiac pain syndromes of the chest, "we can no longer depend with certainly on transient electrocardiographic changes if the electrocardiogram was taken during an attack of pain, as it often is, since extra-cardiac pain induced, for example, by work-ischemia of the forearm muscles, may temporarily produce abnormalities of the T-waves compatible with a diagnosis of coronary insufficiency." In his experience, variability in the

exercise limit over short periods of time is uncommon in coronary artery disease, and "if the distance which the patient can walk fluctuates widely, it is likely that there is an extra-cardiac component in the etiology of pain."

This monograph provides interesting reading but does not seem to be an unusual contribution to the subject.

S. S.

BOOKS RECEIVED

Books received during January are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

The Battle for Mental Health. By JAMES CLARK MOLONEY, M.D. 105 pages; 20.5 × 13.5 cm. 1952. Philosophical Library, New York. Price, $3.50.

Biological Antioxidants: Transactions of the Fifth Conference, November 30—December 1, 1950, New York, N. Y. Edited by COSMO G. MACKENZIE, Department of Biochemistry, University of Colorado School of Medicine. 229 pages; 23.5 × 15.5 cm. (paper-bound). 1951. Sponsored by Josiah Macy, Jr. Foundation, New York. Price, $3.75.

Blood Clotting and Allied Problems: Transactions of the Fourth Conference, January 22–23, 1951, New York, N. Y. Edited by JOSEPH E. FLYNN, Department of Pathology, College of Physicians and Surgeons, Columbia University. 272 pages; 23.5 × 15.5 cm. 1951. Sponsored by Josiah Macy, Jr. Foundation, New York. Price, $4.00.

The Care of the Ageing and Chronic Sick. By A. P. THOMSON, M.C., M.D., Ch.B. (Birmingham), F.R.C.P. (London), Dean of the Faculty of Medicine and Professor of Therapeutics, University of Birmingham, etc.; C. R. LOWE, M.D., Ch.B. (Birmingham), M.R.C.S. (England), L.R.C.P. (London), D.P.H., Lecturer in Public Health, Department of Social Medicine, University of Birmingham; and THOMAS MCKEOWN, B.A. (British Columbia), Ph.D. (McGill), D. Phil. (Oxford), M.D. (Birmingham), M.B., B.S. (London), Professor of Social Medicine, University of Birmingham, etc. 133 pages; 25 × 17 cm. (paper-bound). 1951. Published for the Birmingham Regional Hospital Board by E. & S. Livingstone, Ltd., Edinburgh & London; available in U. S. A. through the Williams & Wilkins Company, Baltimore. Price, $1.50.

The Child in Health and Disease: A Textbook for Students and Practitioners of Medicine. 2nd Ed. By CLIFFORD G. GRULEE, M.D., Rush Professor of Pediatrics, University of Illinois, etc., and R. CANNON ELEY, M.D., Assistant Clinical Professor of Pediatrics, Children's Hospital, Children's Medical Center, Harvard University Medical School, etc. 1,255 pages; 26 × 18 cm. 1952. The Williams & Wilkins Company, Baltimore. Price, $15.00.

Chlorosis: A Retrospective Investigation—Monograph which appeared as a supplementary volume of "Acta Medica Belgica." From the Harry W. Sherman Hematology Research Laboratories, and the Clinical Service of Dr. Raphael Isaacs, Attending Physician in Hematology, Michael Reese Hospital, Chicago, U.S.A. By EMIL SCHWARZ. 199 pages; 24.5 × 16 cm. (paper-bound). 1951.

Clinical Practice in Infectious Diseases, for Students, Practitioners and Medical Officers. 4th Ed. By E. H. R. HARRIES, M.D. Lond., F.R.C.P., Formerly Medical Superintendent, Infectious-Diseases Hospitals Service, London County Council, etc., and M. MITMAN, M.D. Lond, F.R.C.P., Consultant Physician and Medical Superintendent, River Hospitals, Joyce Green, Dartford, etc.; with the

collaboration of IAN TAYLOR, M.D. Lond., M.R.C.P., Senior Medical Officer (Infectious Diseases), Public Health Department, London County Council, etc. 717 pages; 22.5 × 14.5 cm. 1951. The Williams and Wilkins Company, Baltimore. Price, $6.50.

Einführung in die Röntgenologie. By G. F. HAENISCH and H. HOLTHUSEN. 521 pages; 27.5 × 19.5 cm. 1951. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Ganzleinen DM 60.—.

Endocrinology as Related to Embryology: The Selective Action of Endocrine Secretions for Certain Tissues. By ROBERT C. MOEHLIG, M.D., Chief of the Department of Internal Medicine, Harper Hospital, etc. 98 pages; 21.5 × 14 cm. (paper-bound). 1950. Privately printed, Detroit, Michigan.

Heart Disease. 4th Ed. By PAUL DUDLEY WHITE, M.D., Executive Director, National Advisory Heart Council, etc. 1,015 pages; 24 × 16 cm. 1951. The Macmillan Company, New York. Price, $12.00.

Infective Hepatitis: Studies in East Anglia During the Period 1943–47. Medical Research Council Special Report Series No. 273. By F. O. MACCALLUM, A. M. MCFARLAN, J. A. R. MILES, M. R. POLLOCK and C. WILSON. 144 pages; 24.5 × 15 cm. (paper-bound). 1951. His Majesty's Stationery Office, London. Price, 4s 6d net.

Lehrbuch der Röntgendiagnostik. By H. R. SCHINZ, W. E. BAENSCH, E. FRIEDL and E. UEHLINGER. 2,356 pages; 28.5 × 20 cm. (paper-bound). 1951. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, DM 84.—.

Lungenkreislauf. 17. Tagung, Verhandlungen der Deutschen Gesellschaft für Kreislauforschung. Edited by PROF. DR. HANS SCHAEFER. 322 pages; 23 × 15.5 cm. (paper-bound). 1951. Verlag Dr. Dietrich Steinkopff, Darmstadt. Price, Kart. DM 30.—.

A Manual of Parasitology for Medical Students and Beginners. By MARK M. SCHAPIRO, M.D., M.S., Fellow, Royal Society Tropical Medicine and Hygiene, London, etc.; Foreword by SIR PHILIP MANSON-BAHR. 140 pages; 16 × 23 cm. 1951. Grune & Stratton, Inc., New York. Price, $5.50.

Metabolic Interrelations: Transactions of the Third Conference, New York, N. Y., January 8–9, 1951. Edited by EDWARD C. REIFENSTEIN, JR., M.D., Oklahoma Medical Research Institute and Hospital, Oklahoma City, Oklahoma; Editorial Assistant: CLYDELLE BROWNFIELD. 294 pages; 23.5 × 15.5 cm. 1951. Sponsored by Joseph Macy, Jr. Foundation, New York. Price, $4.00.

Modern Dietary Treatment. 3rd Ed. By MARGERY ABRAHAMS, M.A. (Oxon), M.Sc. (Columbia Univ.), Late Dietitian to St. Bartholomew's Hospital, London; and ELSIE M. WIDDOWSON, D.Sc., Ph.D. (Lond.), Department of Experimental Medicine, University of Cambridge. 355 pages; 21 × 13.5 cm. 1951. Baillière, Tindall and Cox, London; available in U. S. A. through The Williams & Wilkins Company, Baltimore. Price, $4.50.

Observations on the General Effects of Injury in Man, with Special Reference to Wound Shock. Medical Research Council Special Report Series No. 277. By R. T. GRANT and E. B. REEVE. 313 pages; 24.5 × 15 cm. (paper-bound). 1951. His Majesty's Stationery Office, London. Price, 8s. 6d. net.

Das Phäochromozytom. By PROF. DR. HEINRICH SACK. 93 pages; 21 × 15 cm. (paper-bound). 1951. Georg Thieme Verlag, Stuttgart. Price, Kartoniert DM 11.70.

Physicians Federal Income Tax Guide, 1952 Edition—For the Preparation of 1951 Returns and 1952 Estimates. By HUGH J. CAMPBELL and JAMES B. LIBERMAN. 112 pages; 28 × 20.5 cm. (paper-bound). 1952. Doniger & Raughley, Great Neck, New York. Price, $2.50.

The Practice of Endocrinology. 2nd Ed. Edited by RAYMOND GREENE, M.A., D.M., M.R.C.P. 389 pages; 25 × 16 cm. 1951. J. B. Lippincott Company, Philadelphia. Price, $12.50.

Should I Retire? By GEORGE H. PRESTON, M.D. 181 pages; 20 × 14 cm. 1952. Rinehart & Company, Inc., New York. Price, $2.50.

Some Common Psychosomatic Manifestations. 2nd Ed. By J. BARRIE MURRAY, M.A., M.D. (Cantab.), M.R.C.P., Diagnostic Physician, Tavistock Clinic, etc. 285 pages; 19 × 13 cm. 1952. Oxford University Press, New York. Price, $3.75.

Standard Nomenclature of Diseases and Operations. 4th Ed. RICHARD J. PLUNKETT, M.D., Editor, and ADALINE C. HAYDEN, R.R.L., Associate Editor. 1,034 pages; 21.5 × 14.5 cm. 1952. Published for The American Medical Association by The Blakiston Company, Philadelphia. Price, $8.00.

X-Ray Interpretation. 2nd Ed. By H. CECIL H. BULL, M.A., M.B., M.R.C.P., Honorary Consulting Radiologist to the Royal Waterloo Hospital, London, and the General Hospital, Southend-on-Sea; with a chapter on Radiography of the Head by JAMES W. D. BULL, M.A., M.B., M.R.C.P., D.M.R., Assistant Radiologist, St. George's Hospital, etc. 406 pages; 22.5 × 14.5 cm. 1952. Oxford University Press, New York. Price, $5.50.

COLLEGE NEWS NOTES

A.C.P. Postgraduate Courses

Four courses—No. 1, Gastro-enterology, San Francisco; No. 2, Current Concepts of Allergy and Associated Disorders, St. Louis; No. 3, Diseases of the Blood Vessels, New York City; No. 4, Clinical Medicine from the Hematologic Viewpoint, Columbus—have already been concluded. Registration in Courses Nos. 1 and 2 was somewhat disappointing, probably due to the fact that members prefer not to be away from their practice during February and early March, and partly due, perhaps, to inadequate time after the distribution of the Final Postgraduate Bulletin. The latter reason could not apply to Course No. 2, because it was fully outlined and publicized adequately in advance. The registration in Courses Nos. 3 and 4 was gratifying, and the courses were most successful.

Courses remaining on the spring schedule:

No. 5, INTERNAL MEDICINE: University of Michigan Medical School, Ann Arbor, Mich., Cyrus C. Sturgis, M.D., F.A.C.P., Director; April 14–18.

This course is now registered to its capacity of sixty.

No. 6, ELECTROCARDIOGRAPHY: Massachusetts General Hospital, Boston, Mass., Conger Williams, M.D., Director; May 12–17.

This course has been registered to its maximum capacity.

No. 7, TRENDS AND NEWER DEVELOPMENTS IN INTERNAL MEDICINE: Hahnemann Medical College and Hospital of Philadelphia, Philadelphia, Pa., Charles L. Brown, M.D., F.A.C.P., Director; May 12–16

This course is still open for registration. It will be an excellent course, and the faculty is chosen from several of the medical schools of Philadelphia.

No. 8, PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE: University of Toronto Faculty of Medicine, Toronto, Ont., Can., Ray F. Farquharson, M.D., F.A.C.P., Director; June 2–6.

This course is a new one in this particular field, held in Canada for the first time. Registration still open.

Course outlines, registration forms, and all salient data may be obtained from the Executive Secretary, The American College of Physicians, 4200 Pine St., Philadelphia 4, Pa. All registrations must be filed with the American College of Physicians, and not with the institutions where the courses are held.

Directory, A.C.P.

The latest directory of The American College of Physicians, though bearing the date of 1951, came from the press and was distributed in early January, 1952. Members who placed pre-publication orders received their copies of the directory in January. A limited number of copies are still available at $5.00 a copy, postpaid. This is the only available reference guide to The American College of Physicians and its members. It will not be revised and republished until the Autumn of 1953.

The following Fellows of the College have become Life Members since the publication of the last issue of the ANNALS:

Dr. Henry C. Crossfield, East Orange, N. J.
Dr. Robin C. Buerki, Detroit, Mich.
Dr. Aleksei A. Leonidoff, Poughkeepsie, N. Y.
Dr. Daniel Marie Green, Chicago, Ill.
Dr. Max H. Rosenblum, Steubenville, Ohio
Dr. Frank R. Mazzola, Jamaica, N. Y.
Dr. Clifford C. Hartman, Pittsburgh, Pa.
Dr. Harold M. Johnson, Honolulu, T. H.
Dr. W. Floyd Keller, Oklahoma City, Okla.
Dr. John W. Martin, Cleveland, Ohio
Dr. John D. Yeagley, York, Pa.
Dr. Robert W. Elliott, Alton, Ill.
Dr. Egon E. Kattwinkel, West Newton, Mass.
Dr. Dwight O'Hara, Boston, Mass.
Dr. Donald F. Closterman, Kingston, Pa.
Dr. John G. Senese, Brooklyn, N. Y.
Dr. Eugene Calvelli, Port Washington, N. Y.
Dr. George Ginsberg, Hoboken, N. J.
Dr. John H. Warvel, Indianapolis, Ind.
Dr. Elmer Friedland, Buffalo, N. Y.
Dr. Morton L. Goldhamer, Cleveland, Ohio
Dr. Charles Roberts Thomas, Chattanooga, Tenn.
Dr. Paul B. Cameron, Pryor, Okla.
Dr. William H. Long, Fargo, N. D.
Dr. Alfred M. Wedd, Sr., Rochester, N. Y.
Dr. Stephen L. Johnson, Evansville, Ind.
Dr. J. Russell Verbrycke, Jr., Washington, D. C.
Dr. Harry D. Williams, Trenton, N. J.
Dr. Herbert R. Edwards, New York, N. Y.
Dr. C. Kelly Canelo, San Jose, Calif.
Dr. Karl O. Von Hagen, Los Angeles, Calif.
Dr. Marine R. Warden, Danville, Ill.
Dr. Joseph B. Whinery, Winter Park, Fla.
Dr. David Schwimmer, New York, N. Y.

The College Life Membership Plan is an equitable and practicable arrangement by which a member may pay his dues during the productive years and while his income is greatest, thus avoiding the burden of dues later in life. Life Membership offers security in advancing years against misfortune which often necessitates relinquishment of one's most cherished professional memberships because of the burden of dues.

The Life Membership fee entitles each Fellow or Master to permanent privileges of membership, to the benefits of the Annual and Regional Sessions, to the ANNALS OF INTERNAL MEDICINE, etc. Each Life Member receives a framed certificate and his name is inscribed in the Life Membership Roll at the College. Life Members are active members for life. All Life Membership fees are deposited in the permanent Endowment Fund of the College and thus contribute to the security of the College as well as to the security of its members. The Life Membership fee is deductible on Federal income tax returns.

Contributions to the James E. Paullin Scholarship Fund

The "James E. Paullin Scholarship Fund" was established by Emory University School of Medicine Alumni on June 2, 1950. The Scholarship Committee was composed of former students, associates and lay friends of the late Dr. Paullin, who was a former Regent and former President of the American College of Physicians. Up to January 1, 1952, $16,235.00 has been contributed to the Fund. The first award in the amount of $500.00 has already been issued for the academic year 1951–52. Selection is made on the basis of need as well as scholastic achievement. The Scholarship Committee plans to use only the income from the Fund, and it is hoped that as it increases the number of awards and the amount of the awards may be increased.

By resolution of the Board of Regents of the American College of Physicians on November 18, 1951, announcement of the Paullin Scholarship Fund was sent to all Regents and Governors of the College, giving them an opportunity, if they so desired, to contribute to the Fund, their remittances to go through the Executive Offices of the College. Thus far the following Regents or Governors or friends have sent contributions, which have been transmitted to the proper authorities:

William C. Blake, Tampa, Fla.
Reginald Fitz, Boston, Mass.
Harold H. Jones, Winfield, Kans.
George H. Lathrope, Morristown, N. J.
Edward R. Loveland, Philadelphia, Pa.
J. Owsley Manier, Nashville, Tenn.
Charles F. Martin, Montreal, Que.
Walter B. Martin, Norfolk, Va.
Pearl M. Ott, Philadelphia, Pa.
Edward C. Reifenstein, Sr., Syracuse, N. Y.
J. O. Ritchey, Indianapolis, Ind.
LeRoy H. Sloan, Chicago, Ill.
B. F. Wolverton, Cedar Rapids, Iowa

The A.C.P. In Hawaii

Dr. Nils P. Larsen, F.A.C.P., College Governor for Hawaii, is putting on a special program for the County Medical Society in Honolulu, during March, the program devoted to the subject of "The Patient with Jaundice." Four different phases will be presented by Dr. John L. Bell (Associate), Dr. Stewart E. Doolittle, F.A.C.P., Dr. A. Worl, and Dr. Frederick L. Giles, F.A.C.P. This program will represent the Annual Regional Meeting of the College in that area.

Gift to the College Library of Publications by Members

Dr. Roscoe L. Pullen, F.A.C.P., Professor of Graduate Medicine and Vice Dean of Tulane University of Louisiana School of Medicine, has presented an autographed copy of his new book, "The Internship," to the College Library of Publications by Members.

This book is an objective consideration of some of the current problems involved in the development and perpetuation of the internship as an educational activity. In presenting his book to the Library, Dr. Pullen mentioned that to the best of his knowledge, it represents the only compilation on the topic ever assembled.

The College Library of Publications by Members is maintained at College Headquarters. Members frequently present copies of their books to the College and thus the library has become a living memorial to the Member-Authors.

A.C.P. Receives Gavel Made from Original Wood Used in the White House

Dr. George F. Schmitt, F.A.C.P., Miami, Fla., secured wood from the White House in 1950 and has presented to the American College of Physicians a gavel made therefrom, and bearing the seal of the United States of America with a plate attesting to the wood having been removed from the White House in 1950, preparatory to the present extensive alterations.

First International Congress, International Diabetes Federation

Those interested in the First International Congress of the International Diabetes Federation to be held at Leyden, the Netherlands, during the second week of July of 1952, are kindly requested to apply for a prospectus to Dr. Elliott P. Joslin, M.A.C.P., Honorary President of the American Diabetes Association, 81 Bay State Rd., Boston 15, Mass. Completed application forms should be in the possession of the Executive Secretary at The Hague on or before April 1, 1952.

Third Pan-American Congress on Gastroenterology to Be Held in Mexico City

The Third Pan-American Congress on Gastroenterology will be held in Mexico City, May 11–17, 1952. The Mexican Gastroenterological Association will hold its First National Congress on the same date. Dr. Abraham Ayala G. is President of the International Congress and Dr. Ramon Flores Lopez, Hospital General, Mexico 9, D. F., is the Secretary General. They have extended a cordial invitation to members of the American College of Physicians to attend this meeting and programs can be obtained from the Secretary General, mentioned above.

American Board of Pediatrics—Oral Examination

The American Board of Pediatrics has announced that an oral examination will be held by the Board in Washington, D. C., May 2–4, 1952.

The 80th Annual Meeting of the American Public Health Association will be held in Cleveland, Ohio, October 20–24, 1952.

The Eighth Annual Meeting of The American College of Allergists

The annual meeting of The American College of Allergists will be held this year at the William Penn Hotel in Pittsburgh, Pennsylvania, on April 7, 8, and 9. The College is offering an unusually practical program for its fellows, members and guests.

In addition to addresses on general topics there will be round tables at luncheons and sectional meetings devoted exclusively to the psychosomatic aspects of the allergic patient, allergy in infants and children, allergic manifestations in the skin, as well as those seen in the eye, ear, nose and throat. Further particulars may be obtained by writing the American College of Allergists, LaSalle Medical Building, Minneapolis 2, Minnesota.

American Heart Association Awards $185,650 to Thirty-seven Research Investigators

Research "brainpower" needed for the development of new and improved methods of treatment, care and prevention of heart disease will receive support from the American Heart Association through the award of thirty-seven Established Investigatorships and Research Fellowships totaling $185,650, according to an announcement made by Dr. Louis N. Katz, F.A.C.P., Chicago, Ill., President of the Association.

The awards are the first of this year's allocations from contributions made by the public to the 1951 Heart Fund. Within the next months additional awards in the form of grants-in-aid to institutions will be announced by the Association to round out the fourth successive year of its national research support program in the cardiovascular field. Apart from this national program, affiliates of the American Heart Association throughout the country make additional research awards in their areas.

Among the established investigators to whom grants have been made are: Dr. J. Russell Elkinton, F.A.C.P., who is continuing his studies in cardiovascular physiology at the University of Pennsylvania School of Medicine, and Dr. John P. Merrill (Associate), who will continue his studies in the further development of the artificial kidney as a therapeutic and investigative tool in cardiovascular and kidney disease at the Peter Bent Brigham Hospital, Boston, Mass.

New Appointments to National Advisory Councils, U.S.P.H.S.

Among twenty-one new members to the seven National Advisory Councils of the U. S. Public Health Service are six Fellows of the American College of Physicians. This announcement was made recently by Surgeon General Leonard A. Scheele, F.A.C.P.

These Councils review all applications for research grants and present their recommendations to the Surgeon General of the U. S. Public Health Service for final approval. The purpose of the grants program is to aid medical and biological research in universities, medical schools and other non-governmental institutions.

The Fellows of the College just appointed are: Dr. Ward Darley, Denver, Colo., National Advisory Mental Health Council; Dr. H. Worley Kendell, Chicago, Ill., National Advisory Neurological Diseases and Blindness Council; Dr. James H. Means, Cambridge, Mass., Ex-President, American College of Physicians, National Advisory Health Council; Dr. Joseph H. Barach, Pittsburgh, Pa., National Advisory Arthritis and Metabolic Diseases Council; Dr. W. Edward Chamberlain, Philadelphia, Pa., National Advisory Cancer Council; Dr. Edward L. Turner, Seattle, Wash., National Advisory Heart Council.

Dr. Raymond Allen Appointed Chancellor of University of California at Los Angeles

Dr. Raymond B. Allen, F.A.C.P., who retired December 31, 1951, as President of the University of Washington, Seattle, has been appointed Chancellor of the University of California at Los Angeles to succeed the late Dr. Clarence A. Dykstra. Dr. Allen was appointed last November by President Truman as head of the United States Psychological Strategy Board and will continue with that work until he takes up his duties in Los Angeles next summer. Dr. Allen formerly was Dean of the Medical Schools at the University of Illinois and Wayne University in Detroit.

Dr. Kenneth W. Chapman, F.A.C.P., has been appointed Medical Officer in Charge of the U. S. Public Health Service Hospital, Lexington, Ky., Surgeon General Leonard A. Scheele, F.A.C.P., recently announced.

In his new position Dr. Chapman will be responsible for the management and operation of a 1,400 bed hospital, the Service's largest. Opened in 1935, it is especially staffed and equipped to treat narcotic addicts as well as patients with neuropsychiatric disorders who are beneficiaries of the Public Health Service. Besides ministering to the direct needs of its patients, the Public Health Service Hospital at Lexington trains psychiatrists and psychiatric nursing personnel and conducts research on narcotic drugs and addiction to them.

The Cincinnati Society of Internal Medicine met February 13 at the University Club. Following the business meeting and buffet luncheon there was a symposium on "The Management of Hypertension: The Point of View of a Physician Who Has Practiced Internal Medicine for 35 Years," by Dr. Hiram B. Weiss, F.A.C.P., "The Point of View of the Investigator," by Eugene B. Ferris, Jr., F.A.C.P., and "The Point of View of the Physician Who Has Recently Completed His Residency Training," by Dr. Harvey Knowles. Dr. Morton Hamburger (Associate) served as Moderator for the discussion period which followed.

Among physicians from the United States recently appointed members of the editorial board of the journal, *Neuropsiquiatria*, published in Buenos Aires by the Argentine Ministry of Public Health, are: Dr. Walter J. Freeman, F.A.C.P., Washington, D. C., and Dr. Matthew T. Moore, F.A.C.P., Philadelphia, Pa.

Brigadier General James S. Simmons, (MC), U.S.A., Retired, F.A.C.P., Dean of the Harvard School of Public Health, Cambridge, Mass., delivered an address in Liberia, January 11, at the dedication of the Liberian Institute of the American Foundation for Tropical Medicine. The institute is an outgrowth of an investigation of disease by the foundation, the Harvard School of Public Health and the Harvard Medical School. Mr. H. S. Firestone, Jr., of the Firestone Tire & Rubber Co., created a $250,000 fund to establish the institute as a memorial to his father.

The Republic of Liberia gave the land. Fifty major industries are contributing to its support, and its operations will be supervised by at least 10 leading university medical schools.

Dr. William Saphir, F.A.C.P., has been appointed Clinical Assistant Professor of Medicine at the University of Illinois College of Medicine.

Dr. E. Rankin Denny, F.A.C.P., formerly of Washington, Ind., is now Chief of Medical Service at the Medical Center Clinic, Bartlesville, Okla.

Dr. Edwin B. Astwood, F.A.C.P., Research Professor of Medicine at Tufts College Medical School, was recently selected as the recipient of one of the nine Borden Awards.

Dr. Astwood's researches in the field of endocrinology, with especial reference to hyperthyroidism, formed the basis for his selection for the 1951 Borden Award by the Association of American Medical Colleges. His most recent achievement has been the preparation of a pituitary adrenocorticotrophic (ACTH) substance 100 times as powerful as any previously used. He earlier established that a third

gonadotrophic hormone, luteotrophin, was essential for corpus luteum function; he developed the drug propylthiouracil for the treatment of hyperthyroidism, thus opening an entirely new field of endocrinology; and isolated and identified 1–5-vinyl-thioöxazolidone, a naturally-occurring goitrogenic compound.

The Colorado Heart Association, the Colorado State Department of Public Health and the University of Colorado School of Medicine sponsored a postgraduate conference on heart disease at Denver, November 14–17, 1951. Dr. Edgar Durbin, F.A.C.P., President of the Colorado Heart Association, was Chairman of the Conference Program Committee. Among the guest speakers were Dr. Paul D. White, F.A.C.P., Boston, Mass., "The Problem of Heart Disease Forty Years Ago and Now," and Dr. George R. Herrmann, F.A.C.P., Professor of Medicine at the University of Texas, Galveston, "Pericarditis; A Five-Year Study" and "Some Studies of Congestive Heart Failure."

An authoritative 12-page instruction booklet on the care of the bed patient's skin, titled "On Guard Against the Wear and Tear of Lying Abed," has just been published. Its purpose is to save time in directing home nursing procedures and for the guidance of graduate or student nurses. It covers: The Skin and Its Functions; Care of the Skin; General and Local Effects of Dry Skin, and Prevention and Care of Skin Irritations Which May Result from Frequent Washing. Copies are available in any desired quantity to Physicians, Hospital Administrators, Graduate Nurses and Nursing Instructors. Distributed without charge by Edison Chemical Co., 30 W. Washington St., Chicago 2, Ill.

Dr. Pascal F. Lucchesi, F.A.C.P., Executive Vice President of the Einstein Medical Center, Philadelphia, Pa., is the winner of the 1952 Philadelphia Fellowship Commission Award.

Dr. Lucchesi was selected because of his efforts to achieve democratic training, personnel and admission practices at the Philadelphia General Hospital, where he was Chief of the Bureau of Hospitals and Medical Director from 1946 to January, 1951.

The award is made annually to a Philadelphian or Philadelphia organization making an outstanding contribution to better intergroup understanding and equality of treatment and opportunity for all racial, religious and nationality groups.

Dr. Charles J. Schreader (Associate), Philadelphia, Pa., was recently appointed a Chief in Medicine at Nazareth Hospital.

Dr. George A. Merrill, F.A.C.P., Brooklyn, N. Y., was recently elected President of the Section of Allergy of the Kings County Medical Society.

Dr. Harry R. Litchfield, F.A.C.P., Brooklyn, N. Y., will present a paper, "Fetal Mortalities in Cesarean Sections," before the Pediatric Section of the American Medical Association Annual Session in Chicago, June 9–13.

Colonel Santino J. Lerro, (MC), U.S.A., (Associate), is presently Surgeon of the Frankfurt Military Post in Germany. In addition, there are present in that area several other medical officers who are members of the American College of Physicians.

OBITUARIES

DR. VERNON C. BRANHAM

Dr. Vernon C. Branham, Associate of the American College of Physicians, was born in Denver, Colo., May 26, 1889. He received his A.B. degree at the University of Denver in 1913. An M.S. degree was earned at the University of Denver in 1914 and an M.A. degree in biological chemistry at Columbia University in 1915. He graduated from the University of Colorado School of Medicine in 1919. He served his internship at St. Elizabeths Hospital in Washington, D. C.

An early interest in outpatient psychiatry was developed. From 1921 to 1923, Dr. Branham was on the staff of the Outpatient Department of the Cornell University Medical College Psychiatric Clinic. During this same period, he served with the East Harlem Health Clinic of New York City. In 1923, he was Senior Assistant Physician at the New York State Psychiatric Institute.

There followed a long period of interest in the problems of the defective delinquent, forensic psychiatry and the psychopathology of criminology. He devoted some 25 years to this field, to which he made major contributions. He was Assistant Superintendent of the Institution for Male Defective Delinquents, Napanoch, N. Y., in 1924; Director of Psychiatric Clinics, State Commission for Mental Defectives, 1924 to 1927; Deputy Commissioner of Correction, New York State, in charge of psychiatric service in prisons, 1930 to 1935; Superintendent, Woodbourne (N. Y.) Correctional Institution, 1935 to 1947. During this period he founded the *Journal of Clinical Psychopathology* and was, until recently, editor and publisher of this journal. He was also an editor of the "Encyclopedia of Criminology," a definitive reference work.

Dr. Branham became associated with the Veterans Administration in 1947 as Assistant Chief of the Outpatient Psychiatry Section and subsequently, in 1947, was made Chief of the Outpatient Psychiatry Section for the Veterans Administration. He played a vigorous role in the shaping and implementation of Veterans Administration outpatient psychiatric policy. He was one of the major architects of the Veterans Administration Mental Hygiene Clinic program.

He was the author of many articles on various aspects of psychiatry. In addition to his writings in the field of forensic psychiatry, he contributed to the literature on child guidance, psychosomatics, mental deficiency, convulsive disorders and other topics.

Dr. Branham was a Diplomate of the American Board of Psychiatry and Neurology and was elected an Associate of the College in 1949. He died October 23, 1951, of coronary occlusion.

JOHN D. SCHULTZ, JR., M.D.,
Veterans Administration

DR. HENRY HARRIS HAFT

Henry Harris Haft, M.D., F.A.C.P., of Syracuse, N. Y., died January 23, 1952, at his home from a long illness due to leukemia.

Dr. Haft was born in Liverpool, England, January 18, 1892, and came to the United States when he was 14 years of age. He graduated from the Syracuse College of Forestry in 1913 and from the Syracuse University College of Medicine in 1917. He was a charter member of Zeta Beta Tau fraternity.

Dr. Haft was a very keen internist with special interest in gastro-enterology. He was very highly respected and regarded by his colleagues in Syracuse. During World War I he served in a hospital in England as Chief of the Medical Service,

and in World War II he was associated with the 52nd General Hospital and was Associated Chief of the Medical Service.

For many years he was associated with the Syracuse University College of Medicine as Clinical Professor of Medicine. Later he became identified with the State University Medical Center at Syracuse, College of Medicine as Clinical Professor of Medicine. He had been Attending Physician at the University Hospital. He was a Diplomate of the American Board of Internal Medicine and was elected a Fellow of the American College of Physicians in 1928.

He was a member of the various Masonic bodies and also of the Rotary Club of Syracuse. Dr. Haft had a very large clientele of patients and his opinion was very highly respected by all those with whom he had contact.

In the death of Dr. Haft the people of Central New York and particularly of Syracuse lost one of its most valuable and respected physicians.

He is survived by his wife, Mrs. Freda Silverman Haft, one son, Dr. David E. Haft of Pittsburgh, Pa., and a daughter, Mrs. Melvin B. Estroff of Lakeland, Fla., five brothers and a sister.

EDWARD C. REIFENSTEIN, SR., M.D., F.A.C.P.,
Governor for Western New York

DR. OSCAR BENWOOD HUNTER, SR.

Oscar Benwood Hunter, Sr., A.B., A.M., M.D., F.A.C.P., was born in Cherrydale, Va., January 31, 1888, and died in Washington, D. C., on December 19, 1951, of a coronary thrombosis. He received his M.D. from George Washington University School of Medicine in 1912 and, interestingly, his A.B. from George Washington University in 1916 and his A.M. in 1917, while actively engaged in teaching at his alma mater.

Dr. Hunter led an exceedingly energetic medical life, beginning it as a teacher, as Instructor in Anatomy at his alma mater in 1913. He was appointed Professor of Histology and Embryology in 1915, and Professor of Bacteriology and Pathology at the same institution from 1916 until 1932, and was Assistant Dean from 1918 until 1930. In 1932 he organized a private laboratory of clinical pathology and continued this enterprise until his death. For many years he was Pathologist at Sibley Memorial Hospital and was Pathologist to the Doctors Hospital from its opening until his death.

From the beginning, he was associated with many of the activities of organized medicine and held many positions in this field, including almost continuous committee assignments in the Medical Society of the District of Columbia and Presidency of the Society in 1928, the Presidency and many other offices in the George Washington Medical Society which was one of his favorite activities. He was President of the American Therapeutic Society in 1938 and 1939, President of the Southern Medical Association in 1948–49, and the First Vice President of the American Medical Association from June, 1951, until his death.

Dr. Hunter was a Diplomate of the American Board of Pathology and a Life Member of the American College of Physicians, having been a Fellow since 1926.

He was always ready to take on new assignments which he considered a service to the profession and had, also, many affiliations with and activities in lay organizations of a public service nature, as evidenced by his Presidency of the Kiwanis Club in 1941. His energy and enthusiasm were unlimited. In all phases of his career, Dr. Hunter was kind and helpful to young men. His convictions and opinions were definite and strong and he did not hesitate to express them when he felt it right to do so. His personality was a vivid one and he gathered about him a wide circle of

friends and admirers. Many people will miss his fellowship and counsel, and organized medicine has lost a vigorous advocate and a strong supporter.

JOHN MINOR, M.D., F.A.C.P.,
Governor for the District of Columbia

DR. SOLOMON S. KAUVAR

In the passing of Dr. Solomon Salkind Kauvar on December 25, 1951, the Rocky Mountain area has lost one of its most prominent internists and important citizens.

Dr. Kauvar was born in Denver, Colo., July 30, 1910. His A.B. degree was obtained from University of Denver in 1929 and his M.D. degree from the University of Chicago School of Medicine in 1934. After serving an internship at the University of Chicago Clinics, Dr. Kauvar served a residency in Medicine at the Montefiore Hospital, New York, N. Y. From 1935 to 1936 he was Libman Fellow in Medicine at the University of Amsterdam, The Netherlands, following which he returned to Denver and entered the practice of Internal Medicine.

In addition to his active interest in clinical medicine, Dr. Kauvar was an outstanding teacher, and at the time of his death was Associate Clinical Professor of Medicine at the University of Colorado School of Medicine and also Chief of the Division of Medicine of the Denver General Hospital, one of the School's teaching hospitals.

In 1947 Dr. Kauvar, with the advent of a new city Administration, temporarily accepted the position of Manager of Health and Charity for the City and County of Denver and from this vantage point completely reorganized the Health Department and the Denver General Hospital, creating one of the most outstanding city health-hospital combinations in the country. In doing this he saw to it that medical, nursing and public health education were intimately woven throughout. After completing this basic organizational work and after obtaining a team of competent administrators to keep the program going, Dr. Kauvar returned to his practice. His active interest in the program was continued; he accepted membership upon the newly created Board of Health and Hospitals, of which he was President at the time of his death.

It is largely because of the results of Dr. Kauvar's efforts that the General Clinic—oriented to the continuing care of the non-hospitalized patient, under the joint sponsorship of the City of Denver and the University of Colorado—was made possible, thus providing a frame of reference for the education of physicians, nurses and social workers, which the community's civic, educational and medical leaders feel may exert a strong influence on the future of both medical and health education and service.

Dr. Kauvar was elected a Fellow of the American College of Physicians in 1945. He was a Diplomate of the American Board of Internal Medicine and a member of the American Medical Association and its component societies. As would be expected of an internist with a large consulting practice, Dr. Kauvar was active in the staff activities of all of the Denver hospitals.

The absence of Dr. Kauvar's wise counsel and leadership is keenly felt.

WARD DARLEY, M.D., F.A.C.P.,
Governor for Colorado

DR. LOUIS CHARLES ROSENBERG

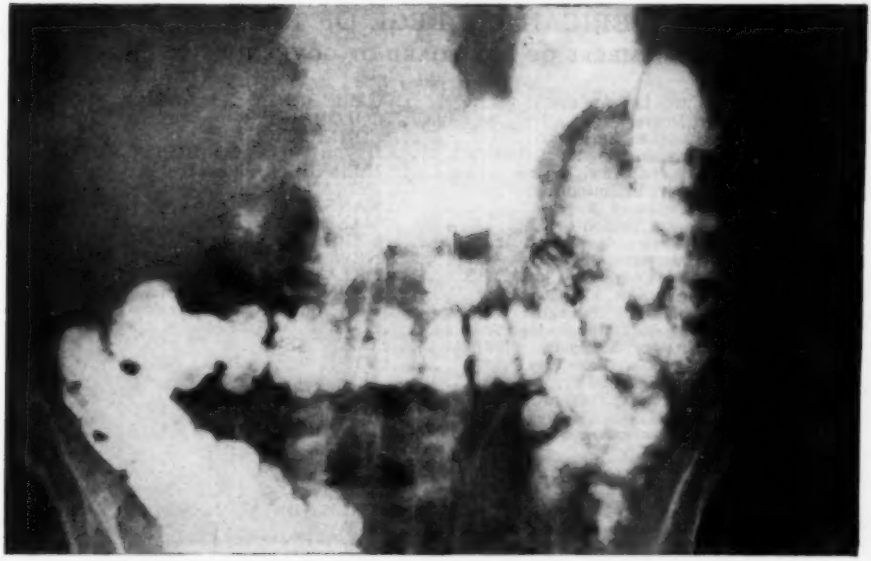
Louis Charles Rosenberg, M.D., F.A.C.P., was born in New Haven, Conn., October 12, 1892, and died in Newark Beth Israel Hospital on November 3, 1951, of acute leukemia, at the age of 59. He had married only in the recent past and is survived by his widow.

After receiving his M.D. degree in 1916 from the George Washington University School of Medicine, Dr. Rosenberg took postgraduate training in Pediatrics at Columbia University College of Physicians and Surgeons, 1920–1921. At the time of his death, he was co-Director of the Pediatric Division at Newark Beth Israel Hospital and Director of the Pediatric Service at the Essex County Hospital for Contagious Diseases in Belleville. He also was Consultant Pediatrician at Babies' Hospital-Coit Memorial in Newark.

Dr. Rosenberg was a rich contributor to the medical literature. His monographs on Diet in Children and X-Ray Treatment for Lymphadenitis were outstanding. During World War I he served overseas in the Medical Corps, U. S. Army, attached to Base Hospital No. 63. He was a member of the American Medical Association, his State and County Medical Associations, as well as the American Heart Association, the American Diabetes Association and the Association for the Study of Internal Secretions. He was elected a Fellow of the American College of Physicians in 1930.

Dr. Rosenberg's genial personality and wise counsel will be missed by his many friends and his colleagues.

Edward C. Klein, Jr., M.D., F.A.C.P.,
Governor for New Jersey



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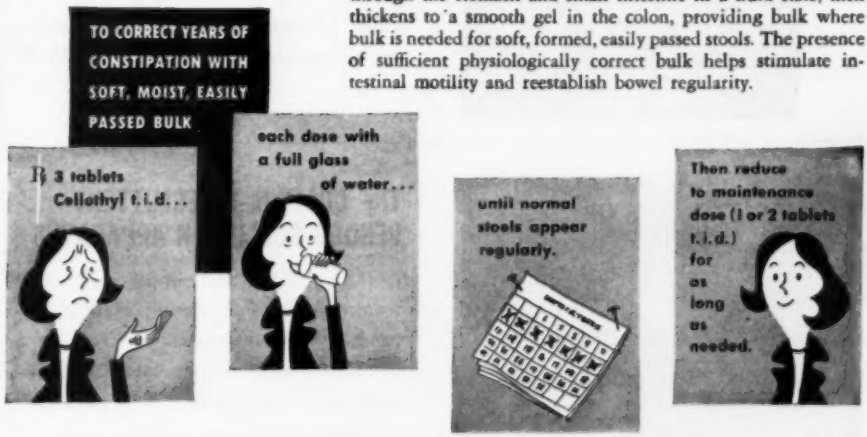
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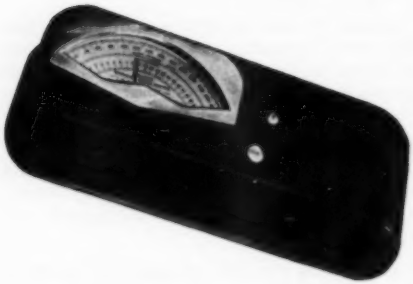

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